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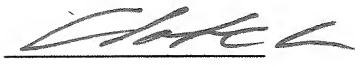

For and on behalf of RWS Group Ltd

The 10th day of October 2007

FEDERAL REPUBLIC OF GERMANY

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Priority Certificate
for the filing of a Patent Application

File Reference:	102 38 045.7
Filing date:	20 August 2002
Applicant/Proprietor:	Merckle GmbH Chemisch –pharmazeutische Fabrik, Ulm/DE
Title:	2-Thio-substituted imidazole derivatives and their use in pharmacy
IPC:	C 07 D, A 61 K

The attached documents are a correct and accurate reproduction of the original submission for this application.

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2-Thio-substituted imidazole derivatives and their use in pharmacy

The present invention relates to 2-thio-substituted imidazole derivatives having immunomodulating and cytokine-release-inhibiting action, to pharmaceutical compositions comprising these compounds and to their use in pharmacy.

Pharmacologically active imidazole compounds with anti-inflammatory activity are already known. Thus, inter alia, compounds having 4.5-di(hetero)arylimidazole moieties have been examined more closely, and various pharmaceutical actions thereof have been described. Also known are compounds which are substituted in the 2-position. US patent 4.585.771 discloses 4.5-diphenylimidazole derivatives which are substituted in the 2-position by a pyrrolyl, indolyl, imidazolyl or thiazolyl radical and which have anti-inflammatory and antiallergic activity. US patents 4.528.298 and 4.402.960 describe 4.5-di(hetero)arylimidazole derivatives which are substituted in the 2-position via a thio, sulfinyl or sulfonyl group by a phenyl, pyridyl, N-oxypyridyl, pyrimidyl, thiazolyl or thienyl radical and which have anti-inflammatory and antiallergic activity. US patents 4.461,770 and 4.584.310 describe 4-(5-aryl)-5-(4-heteroaryl)imidazole derivatives which are substituted in the 2-position via a thio, sulfinyl or sulfonyl group by a substituted or unsubstituted aliphatic hydrocarbon and which, inter alia, have anti-inflammatory action. Imidazole compounds having immunomodulating and cytokine-release-inhibiting action are described in DE 101 07 683 and DE 102 22 103.

WO 00/17192 (DE 198 42 833) relates to 4-heteroaryl-5-phenylimidazole derivatives which are substituted in the 2-position by a phenylalkylthio group. These compounds act as anti-inflammatories and inhibitors of cytokine release. WO 99/03837 and WO 93/14081 describe 2-substituted imidazoles which inhibit the synthesis of a number of inflammatory cytokines. The compounds described in WO 93/14081 have in the 2-position, attached via a sulfur atom, a phosphorus-containing substituent or an aryl or heteroaryl substituent. WO 91/10662 describes imidazole derivatives which inhibit the acyl-coenzyme A:cholesterol-O-acyl transferase and binding of thromboxane TxA_2. WO 95/00501 describes imidazole derivatives which can be used as cyclooxy-

genase inhibitors. The imidazole derivatives described in DE 28 23 197 A have an antiinflammatory, antiallergic and immunostimulating effect.

J. Med. Chem. 1996, 39, 3927-37 describes compounds having 5-lipoxygenase- and cyclooxygenase-inhibiting action, 2-(4-methylsulfinylphenyl)-4-(4-fluorophenyl-5-(pyrid-4-yl)imidazole also having cytokine-inhibiting action.

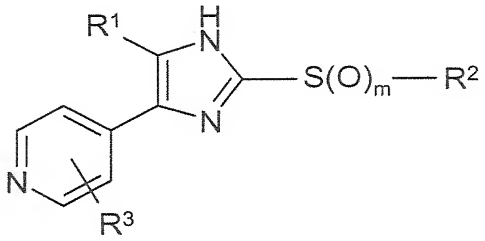
Further 2-thio-substituted imidazole derivatives are described in JP 01-040 467, Acta Chim. 1969, 61, 69 - 77 and J. prakt. Chem. 1972, 314, 785 – 792 and DE 101 14 775.

In spite of the fact that numerous compounds are known, there is therefore still a need for compounds having anti-inflammatory action which inhibit cytokine release.

It is an object of the invention to provide such compounds.

Surprisingly, it has now been found that certain 2-substituted imidazole derivatives have high immunomodulating and/or cytokine-release inhibiting activity.

Accordingly, the present invention provides 2-thio-substituted imidazole derivatives of the formula I



in which

R^1 is C_1-C_6-alkyl, C_3-C_7-cycloalkyl or aryl which is unsubstituted or substituted by a halogen atom;

R^2 is selected from the group consisting of

a) aryl-C_1-C_4-alkyl, where the aryl radical may have one, two or three substituents independently of one another selected from the group consisting of C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, C_1-C_6-alkylsulfanyl, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl and hydroxyl, and

b) C_1-C_6-alkyl which is unsubstituted or substituted by CN; and

c) C_3-C_7-cycloalkyl;

R^3 is selected from the group consisting of

a) NR^4R^{10}

b) NR^7COR^8,

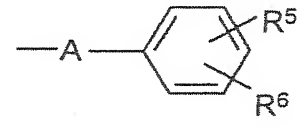
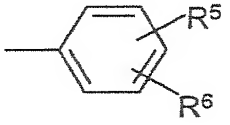
c) halogen, and

d) C_1-C_6-alkoxy,

e) C_1-C_6-alkylthio-

where R^3 is not OH, halogen, C_1-C_6-alkylthio or C_1-C_6-alkoxy if R^2 is phenyl-C_1-C_4-alkyl and the phenyl radical has a C_1-C_6-alkylsulfanyl, C_1-C_6-alkylsulfinyl or C_1-C_6-alkylsulfonyl substituent;

R^4 is H;

R^{10} is  or 

R^5 and R^6, which may be identical or different, are H, halogen, C_1-C_6-alkoxy, or C_1-C_6-alkyl;

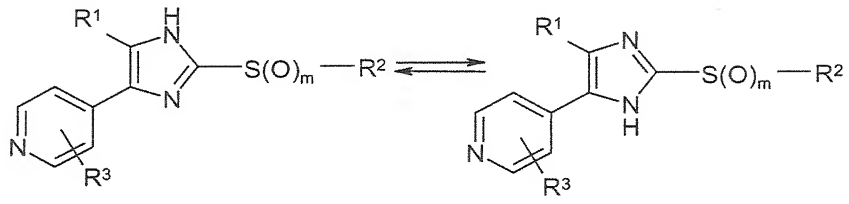
R^7 is H, C_1-C_6-alkyl or benzyl;

R^8 is C_1-C_4-alkyl, C_3-C_6-cycloalkyl or phenyl, it being possible for the phenyl group to have one or two substituents which are chosen independently from one another from the group consisting of C_1-C_4-alkyl, C_1-C_4-alkoxy and halogen;

A is straight-chain or branched C_1-C_6-alkylene, C_2-C_6-alkenylene or C_3-alkynylene and

m is 0, 1 or 2.

If the compounds according to the invention have centers of asymmetry, the scope of the invention includes both racemates and optical isomers (enantiomers, diastereomers). In the compounds according to the invention, the following tautomeric equilibrium may be present:



The invention embraces both tautomeric forms.

The invention also embraces the physiologically acceptable salts of the compounds of the formula I. In the present case, these are in particular acid addition salts. For acid addition salts, what is used are inorganic acids, such as hydrochloric acid, sulfuric acid or phosphoric acid, or organic acids, such as tartaric acid, citric acid, maleic acid, fumaric acid, malic acid, mandelic acid, ascorbic acid, gluconic acid and the like.

The term "alkyl" (also in combination with other groups, such as phenylalkyl, alkylsulfonyl, etc.) embraces straight-chain and branched alkyl groups having 1 to 6 or 1 to 4 carbon atoms, such as methyl, ethyl, n- and isopropyl, n-, iso- and t-butyl, sec-butyl, n-pentyl, isoamyl, neopentyl and n-hexyl.

The term "aryl" embraces aromatic ring systems, such as phenyl or naphthyl.

The term "halogen" represents a fluorine, chlorine, bromine or iodine atom, in particular a fluorine or chlorine atom.

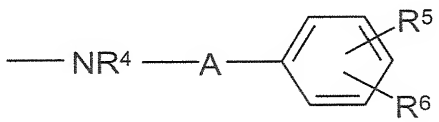
C_3-C_7-cycloalkyl groups are cyclopropyl, cyclobutyl, cycloheptyl and, in particular, cyclopentyl and cyclohexyl.

Phenyl-C_1-C_4-alkyl is in particular benzyl or phenylethyl.

R^1 is preferably a phenyl radical and in particular a halogen-substituted phenyl radical, a fluorine-substituted phenyl radical being particularly preferred. The halogen radical is preferably in the 4-position.

R^2 is preferably a benzyl or C_1-C_6-alkyl radical, where the phenyl group of the benzyl radical may be substituted as indicated above. Preferred substituents are C_1-C_6-alkylsulfanyl, C_1-C_6-alkylsulfinyl and C_1-C_6-alkylsulfonyl.

R^3 is preferably the radical of the formula

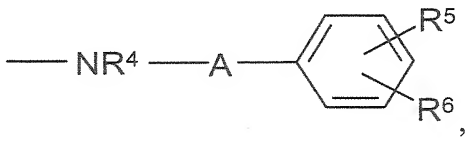


in which R^4, R^5 and R^6 and also A are as defined above. R^5 and R^6 are preferably H, methyl, methoxy or chlorine. If the phenyl ring of this group is substituted, the radicals R^5 and R^6 are preferably located in the 3- and/or 4-position.

A is preferably C_1-C_2-alkylene and in particular ethylidene.

m is preferably 0.

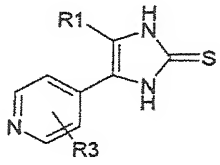
A particularly preferred embodiment are the compounds of the formula I in which R^1 is 4-fluorophenyl, R^2 is C_1-C_6-alkyl or benzyl, where the phenyl group of the benzyl radical may be substituted as indicated above; R^3 is the radical of the formula



where R^4, R^5, R^6 and A are as defined above, and m is 0.

The compounds according to the invention can be prepared in a corresponding manner according to the processes described in the state of the art mentioned at the outset, in particular WO 00/17192. The preparation according to the following two-step process has been found to be particularly expedient. In the first step, a substituted imidazole-2-thione of the formula II is initially prepared. In the second step, this is then reacted such that the desired substituent R^2 is introduced.

1) Preparation of the imidazole-2-thiones of the formula



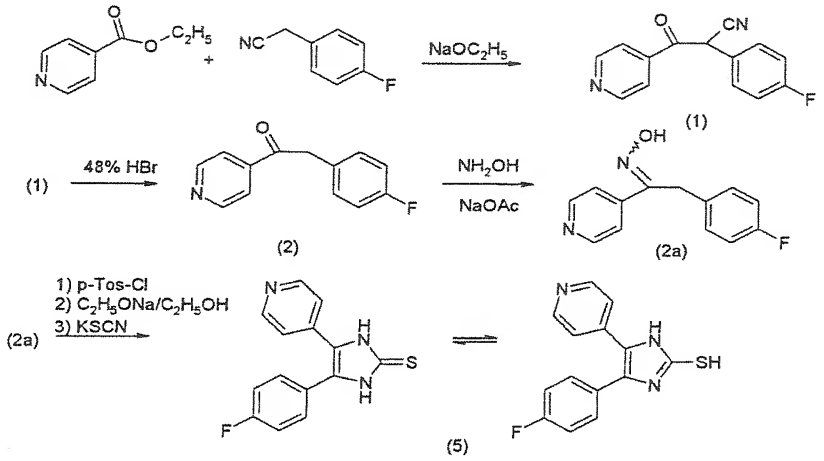
The imidazole-2-thiones where R^3 = H are prepared according to process 1. By way of example, the process is illustrated for compounds in which R^1 is 4-fluorophenyl and R^3 is H. Imidazole-2-thiones with other R^3 radicals (R^3 = F, Cl, Br) are prepared according to process 2.

Process 1

The synthesis of the substituted imidazole-2-thiones where R^3 = H is carried out according to the course of the reaction of scheme 1, using ethyl isonicotinate and 4-fluorophenylacetonitrile as starting materials.

The starting materials are converted in a condensation reaction with the aid of metallic sodium in an alcohol, for example ethanol, into 2-cyano-2-(4-fluorophenyl)-1-(4-pyridyl)ethanone (compound 1). The cyano group is then removed by hydrolysis, for example with hydrobromic acid, and decarboxylation, giving 2-(4-fluorophenyl)-1-(4-pyridyl)ethanone (compound 2). In the next step, compound 2 is converted by treatment with ammonium chloride/sodium acetate in an alcoholic solvent, such as methanol, into the oxime (2a). By reaction with p-toluenesulfonyl chloride in pyridine, the latter is converted into the tosylate. From the tosylate, the compound (5) is obtained by treatment with sodium ethoxide and reaction of the azirene intermediate formed with potassium thiocyanate.

Scheme 1:
Synthesis of the thiones

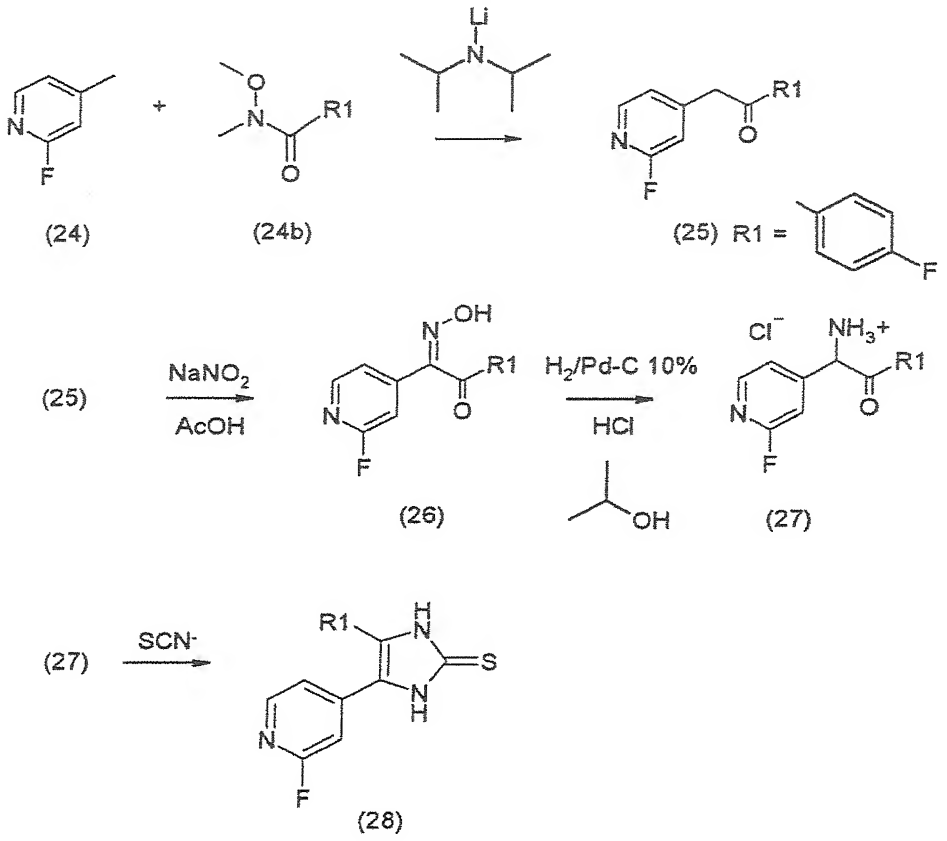


Process 2:

The preparation of the compounds according to the invention in which the pyridine radical has an amino or amido substituent is carried out according to scheme 2 via corresponding 2-halopyridyl-substituted imidazolthiones (process 2). The preparation

of these imidazolthiones is illustrated using the 2-fluoro-substituted pyridinine compound (R^3 = 2-F) where R^1 = p-fluorophenyl as an example. Imidazolthiones carrying, in position 4, alkyl and cycloalkyl radicals (R^1 = C_1-C_4-alkyl, C_3-C_7-cycloalkyl) are obtained in an analogous manner starting with the appropriately substituted 2-fluoro-γ-picoline ketones.

Scheme 2:



γ-Picoline (R^3 = H) and the halogen- (R^3 = F(24), Cl, Br, I), methoxy- (24, R^3 = OCH_3) and methylthio- (24, R^3 = SCH_3) substituted γ-picolines are lithiated in the γ-methyl group with exclusion of moisture, in solvents suitable for this purpose, such as hydrocarbons, ethers and mixtures thereof (for example hexane, tetrahydrofuran, ethylene glycol, dimethyl ether), using lithium diisopropylamide (LDA) and then condensed

with suitable carboxylic acid derivatives (R^1-COOR, R^1-$CONR_2$, R^1-CN c.f. example 20). Here, the amides of the N,O-dimethylhydroxylamine have been found to be particularly suitable. Using nitrites and bases, for example amyl nitrite /sodium methoxide, or using alkali metal nitrite and acid, the γ-picolyl ketones (25) formed are nitrosated in the γ-picolyl position. The reaction of the γ-picolyl ketone, dissolved in glacial acetic acid, with aqueous sodium nitrite solution has been found to be particularly advantageous. During this reaction, the nitrosoketones are converted completely into the tautomeric oxime ketones (26).

The oxime ketones are reduced in alcoholic solution in the presence of hydrogen and mineral acids, for example HCl, using palladium-on-carbon, to give the ammonium salts of the amine ketones (27) (c.f. example 23b).

Alternatively, other oxime ketones can be reduced in alcoholic solution in the presence of mineral acids, for example H_2SO_4, using zinc dust, to give the corresponding amine ketones (c.f. example 23f).

These ammonium ketone compounds afford, after action of thiocyanates, for example potassium thiocyanate, in dry dimethylformamide (DMF) with heating under reflux, the imidazolethiones of the formula II where R^3 = F (28), Cl, Br, OR or SR, as yellow solids (c.f. example 24b).

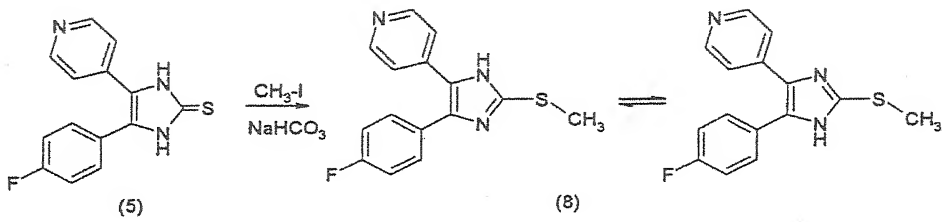
2) Preparation of the 2-thioimidazole compound

The imidazolethione compounds of the formula II obtained according to process 1 or 2 are, by substitution of the sulfur atom in the 2-position, converted into the compounds of the formula I according to the invention. The substitutions, as shown in an exemplary manner for some compounds in scheme 3, are carried out in a known manner using a nucleophilic substitution reaction. Here, the compound 5 or 28 is reacted with R^2-X in an inert polar solvent, such as an alcohol. X is an easily exchangeable group, such as Hal, in particular Cl, Br, I, methylsulfonyl, tosyl, etc. Suitable processes are known to the person skilled in the art and described, for example, in WO 00/17192, EP 0 372 445 and US 4.440,776. The compounds R^2-X are known or can be prepared by known processes as described, for example, in WO 00/17192.

Scheme 3:

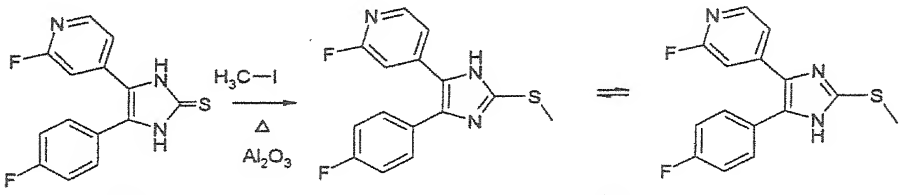
Substitution of the sulfur by alkyl halides and arylalkyl halides or alcohol sulfonates.

3.1.



(5) (8)

3.2.



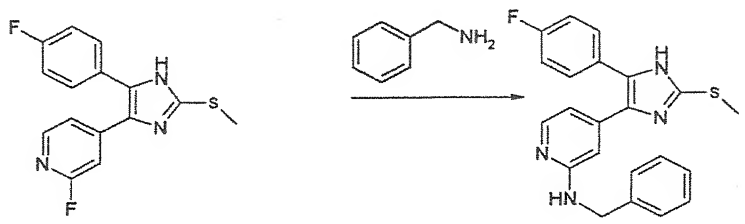
(28) (29)

Compounds according to the invention in which R^3 is an amino or amido substituent (R^3 = NR^4R^{10}, NR^7COR^8) are prepared from 2-thioimidazoles using 4(5)-(2-halopyridin-4-yl) substitution. The process is illustrated in scheme 4 using the 2-benzylamino (R^3 = NH-CH_2Ph) and the 2-benzamido-pyridine compound (R^3=NH-COPh) where R^1 = p-fluorophenyl as an example (c.f. example 25f).

The starting materials (28) can be prepared by the process described above.

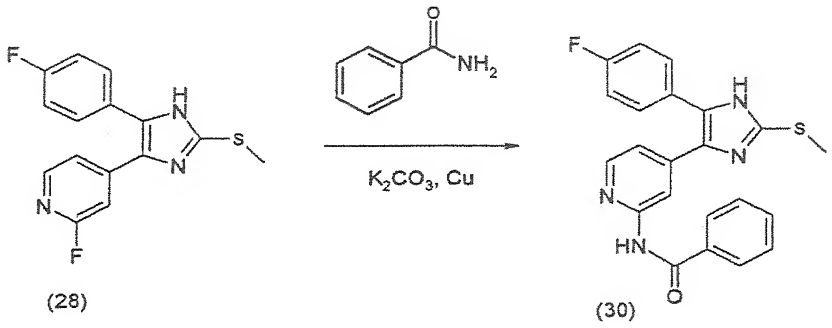
Scheme 4:

4a: 4-(2-Aminopyridin–4-yl)-substituted 2-thioimidazoles



(28) (29)

4b: 4-(2-Amidopyridin–4-yl)-substituted 2-thioimidazoles



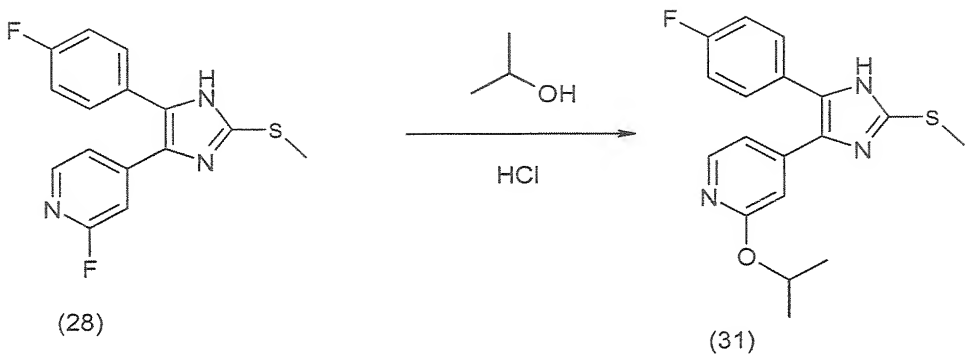
The reaction is expediently carried out in the amine or amide in question, which is preferably employed in an amount of from 5 to 20 mole equivalents per mole equivalent of the compound (28). The reaction temperature is generally in the range from 100 to 200°C. If desired, it is also possible to use an inert solvent, such as dioxane, dimethylformamide, diethylacetamide, methylpyrrolidone, etc., and appropriate additives, such as alkali metal carbonates or copper powders (to neutralize acid equivalents released or to catalyze the elimination of halogen).

The compounds according to the invention which, in R^3, have an alkoxy substituent (R^3 = O-C_1-C_6-alkyl) are prepared, starting with the 4(5)-(2-halopyridin-4-yl)-substituted 2-thioimidazoles. The process is illustrated in scheme 5, using the 2-isopropyloxypyridinine compounds (R^3 = $OCH(CH_3)_2$) where R^1 = p-fluorophenyl as an example.

The starting materials (28) can be prepared by the processes described above.

Scheme 5:

4-(2-Alkoxypyridin–4-yl)-substituted 2-thioimidazoles



(28) (31)

The reaction is expediently carried out in the alcohol, which is preferably used in an amount of from 5 to 20 mole equivalents per mole equivalent of the compound (28), in the case of lower alcohols also up to one hundred mole equivalents, in the presence of a strong acid, such as HCl or trifluoroacetic acid, methanesulfonic acid, etc. The reaction temperature is generally within the boiling range of the lower alcohols, in the case of higher alcohols in the range from 100 to 200°C. It has been found to be favorable, for example, to saturate the alcohol with gaseous HCl, or to re-saturate during the reaction.

Alternatively, the exchange of fluorine for alkoxy in the 2-position of the pyridyl substituent can be carried out at an earlier stage in the synthesis, for example at the stage of the oxime ketones or the amine ketones. In these cases, the reactions proceed under comparable conditions to those just described (c.f. example 22c) of the intermediate 28.

In vitro and *in vivo*, the compounds according to the invention show immunomodulating and cytokine-release inhibiting action. Cytokines are proteins such as TNF-α and IL-β which play an important role in numerous inflammatory disorders. The compounds according to the invention are, by virtue of their cytokine-release-inhibiting action, suitable for treating disorders which are associated with a disturbance of the immune system. They are suitable, for example, for treating autoimmune disorders, cancer, rheumatoid arthritis, gout, septic shock, osteoporosis, neuropathic pain, the spread of HIV, HIV dementia, viral myocarditis, insulin-dependent diabetes, periodontal disorders, restenosis, alopecia, T-cell depletion associated with HIV infections or AIDS, psoriasis, acute pancreatitis, rejection reactions of allogenic transplants, allergic pneumonia, arteriosclerosis, multiple sclerosis, cachexia, Alzheimer's disease,

stroke, ictus, colitis ulcerosa, morbus Crohn, inflammatory bowel disease (IBD), ischemia, congestive heart failure, pulmonary fibrosis, hepatitis, glioblastoma, Guillain-Barre syndrome, systemic lupus erythematodes, adult respiratory distress syndrome (ARDS) and respiratory distress syndrome.

The compounds according to the invention can be administered either as individual therapeutically active compounds or as mixtures with other therapeutically active compounds. The compounds can be administered on their own; in general, however, they are formulated and administered in the form of pharmaceutical compositions, i.e. as mixtures of the active compounds with suitable pharmaceutical carriers or diluents. The compounds or compositions can be administered orally or parenterally; preferably, they are administered in oral dosage forms.

The type of pharmaceutical composition or carrier or diluent depends on the desired administration form. Oral compositions, for example, can be present as tablets or capsules and may comprise customary excipients, such as binders (for example syrup, gum arabic, gelatin, sorbitol, tragacanth or polyvinylpyrrolidone), fillers (for example lactose, sugar, cornstarch, calcium phosphate, sorbitol or glycerol), glidants (for example magnesium stearate, talc, polyethylene glycol or silica), disintegrants (for example starch) or wetting agents (for example sodium lauryl sulfate). Liquid oral preparations can assume the form of aqueous or oily suspensions, solutions, emulsions, syrups, elixirs or sprays and the like. They can also be present as a dry powder which is reconstituted using water or another suitable carrier. Such liquid preparations may comprise customary additives, for example suspending agents, flavors, diluents or emulsifiers. For parenteral administration, it is possible to use solutions or suspensions with customary pharmaceutical carriers.

The compounds or compositions according to the invention can be administered to mammals (man or animal) in a dose of from about 0.5 mg to 100 mg per kg of body weight per day. They may be administered in one individual dose or in a plurality of doses. The activity spectrum of the compounds as inhibitors of cytokine release was examined using the test systems below, as described by C. Donat and S. Laufer in Arch. Pharm. Pharm. Med. Chem. 333, Suppl. 1, 1-40. 2000.

In vitro test with human whole blood

The test substance is added to samples of human potassium-EDTA whole blood (of 400 µl each) and the samples are preincubated in a CO_2 incubator (5% CO_2; 95% moisture-saturated air) at 37°C for 15 min. The samples are then stimulated with 1 µg/ml of LPS (*E.coli* 026:B6) at 37°C in a CO_2 incubator (5% CO_2; 95% moisture-saturated air) for 4 hours. The reaction is stopped by placing the samples on ice, adding DPBS buffer and then centrifuging at 1000 g for 15 min. The amount of IL-1β and TNFα in the plasma supernatant is then determined by ELISA.

In vitro test with PBMCs

1) The mononuclear cells (PBMCs) from human potassium-EDTA whole blood, diluted 1:3, are isolated by density gradient centrifugation (Histopaque®-1.077). The cells are washed twice with DPBS buffer, resuspended in macrophage SFM medium and adjusted to a cell count of 1×10^6 cells/ml.

The resulting PBMCs suspension (samples of in each case 390 µl) and the test substance are preincubated at 37°C in a CO_2 incubator (5% CO_2; 95% moisture-saturated air) for 15 min. The samples are then stimulated with in each case 1 µl/ml of LPS (*E.coli* 026:B6) at 37°C in a CO_2 incubator (5% CO_2; 95% moisture-saturated air) for 4 hours. The reaction is stopped by placing the samples on ice, adding DPBS buffer and then centrifuging at 15 880 g for 12 min. The amount of IL-1β and TNFα in the plasma supernatant is then determined by ELISA.

2) Kinase assay

At 37°C, microtiter plates were coated for one hour with 50 µl of ATF2 solution (20 µg/ml). The plates were washed three times with water, and 50 µl of kinase mixture (50 mM tris-HCl 10 mM $MgCl_2$, 10 mM β-glycerol phosphate, 10 µg/ml of BSA, 1 mM DTT, 100 µM ATP, 100 µM Na_3VO_4, 10 ng of activated p38α) with or without inhibitor were added into the wells, and the plates were incubated at 37°C for 1 hour. The plates were washed three times and then

incubated with phosphorus-ATF-2 antibody at 37°C for one hour. The plates were once more washed three times, and goat-antirabbit IgG labeled with alkaline phosphatase was added at 37°C for one hour (to fix antibody-phosphorylated protein/substrate complex). The plates were washed three times, and the alkaline phosphatase/substrate solution (3 mM 4-NPP, 50 mM $NaHCO_3$, 50 mM $MgCl_2$, 100 µl/well) was added at 37°C for 1.5 hours. Formation of 4-nitrophenolate was measured at 405 nm using a microtiter plate reader. The IC_{50} values were calculated.

The results of the *in vitro* tests are shown in table 1 below.

Table 1: Test results

Compound No.	IC_{50} (μM) p 38	IC_{50} (μM) TNF-α	PBMCA IL-1β	K_{50} (μM) TNF-α	Whole blood IL-1β
25a		2.2	0.35		
25b	3.8	2.8	0.30		
25c	8.7	4.6	2.7	7.2	2.2
25d		1.9	0.15		
25e		3.1	0.50		
25f	0.65	0.63	0.108		
25g	0.79	0.64	0.056		
25h	0.83	0.67	0.085	17.3	22.3
25i	0.95	0.50	0.15	14.8	13.3
25j	0.70	0.72	0.23		
25k	0.13	0.34	0.030		
25l	0.24	0.35	0.031	14.9	17.1
25m	0.38	0.16	0.039	2.7	0.99
25n	0.34	0.17	0.041		
25o	0.90	0.37	0.044		
26a		60.0	1.8		
26b	4.2	40.5	2.9		
26c	1.42	3.2	0.20		
26d	0.38	2.7	0.045		
26e		21.0	0.18		
27a		12.0	2.1		
27b	9.3	6.9	2.45		
27c	1.45	2.0	0.47		
27d	0.27	0.91	0.040	10.0	15.7

Examples

Example 1

a) 4-(4-Fluorophenyl)-5-pyridin-4-yl-1,3-dihydroimidazole-2-thione

2-(4-Fluorophenyl)-3-hydroxy-3-pyridin-4-ylacrylonitrile (a1)

A mixture of ethyl isonicotinate (75.8 g; 0.5 mol) and 4-fluorophenylacetonitrile (67.6 g; 0.5 mol) was added dropwise to a solution of metallic sodium (17.3 g; 0.7 mol) in absolute ethanol (250 ml). The reaction mixture was stirred at 100°C for 15 min. The reaction mixture was then cooled in an ice bath, and 600 ml of distilled H_2O were added. When the mixture was acidified with concentrated HCl (90 ml), the hydrochloride of **a1** was obtained as yellow precipitate at pH 1. The precipitate was filtered off, washed with H_2O and dried under reduced pressure over P_2O_5. M.p. 226°C

2-(4-Fluorophenyl)-1-pyridin-4-ylethanone (a2)

A solution of **a1** (40.6 g; 0.15 mol) in 48% strength hydrobromic acid (130 ml) was stirred under reflux for 19 h. The mixture was cooled in an ice bath, and the precipitate obtained (4-fluorophenylacetic acid) was filtered off and washed with H_2O. When the filtrate was neutralized with ammonia water (80 ml) **a2** was obtained as a dark-green precipitate which was filtered off, washed with H_2O and dried under reduced pressure over P_2O_5: light-gray/beige powder. M.p. 215°C

2-(4-Fluorophenyl)-1-pyridin-4-ylethanone oxime (a3)

Sodium acetate (36.1 g; 0.44 mol) and hydroxylamine hydrochloride (22.0 g; 0.32 mol) were introduced into a suspension of **a2** (21.5 g; 0.1 mol) in 50% strength methanol (350 ml). The reaction mixture was stirred under reflux for 1 h. When the clear solution was cooled in an ice bath, **a3** was obtained as a beige precipitate which was filtered off, washed with H_2O and dried under reduced pressure over

P_2O_5.
M.p. 155°C

2-(4-Fluorophenyl)-1-pyridin-4-ylethanone, O-[(4-methylphenyl)sulfonyl]oxime (a4)

Under an atmosphere of argon, **a3** (10.1 g; 0.04 mol) was dissolved in absolute pyridine (50 ml). The solution was cooled to 6°C, and toluenesulfonyl chloride (10.1 g; 0.05 mol) was added a little at a time. After the addition had ended, the reaction mixture was stirred at room temperature for 20 h. The mixture was then poured into 500 ml of ice-water. The precipitate **(a4)** was filtered off, washed with cold H_2O and dried in a drying cabinet at 50°C. M.p. 201°C

4-(4-Fluorophenyl)-5-pyridin-4-yl-1,3-dihydroimidazole-2-thione (1a).

Under an atmosphere of argon, a solution of a4 (10.0 g; 0.03 mol) in absolute ethanol (56 ml) was cooled to 5°C, and a freshly prepared solution of metallic sodium (0.75 g; 0.03 mol) in absolute ethanol (30 ml) was added dropwise. The reaction mixture was stirred at 5°C for 5 h. After addition of diethyl ether (500 ml), stirring was continued for 30 min. The precipitate (TosOH) was filtered off and washed with diethyl ether (4 × 50 ml). The combined ethereal phase was extracted with 10% strength hydrochloric acid (3 × 90 ml). The aqueous extract was concentrated to a volume of about 40 ml, and potassium thiocyanate (5.0 g; 0.05 mol) was added. The reaction mixture was stirred under reflux for 1 h. When the mixture was neutralized with 5% strength sodium bicarbonate solution (270 ml), a5 was obtained as a beige precipitate which was filtered off, washed with H_2O and dried in a drying cabinet at 60°C. Yield 5.6 g (79%); m.p. 382°C

^{1}H-NMR (DMSO-d_6): δ (ppm) 7.1 (m, 2H, 4-F-Ph), 7.3 (m, 2H, 4-Pyr), 7.5 (m, 2H, 4-F-Ph), 8.5 (m, 2H, 4-Pyr), 12.7 (d, 2H, exchangeable, NH)

The following compounds were obtained in a corresponding manner:

1c: 4-(4-chlorophenyl)-5-pyridin-4-yl-1,3-dihydroimidazole-2-thione

1d: 4-(4-bromophenyl)-5-pyridin-4-yl-1,3-dihydroimidazole-2-thione

1e: 4-phenyl-5-pyridin-4-yl-1,3-dihydroimidazole-2-thione

Example 2

1-Chloromethyl-4-methylsulfanylbenzene (2)

4-Methylsulfanylbenzyl alcohol (30.5 g; 0.2 mol) was dissolved in dichloromethane (180 ml). A solution of thionyl chloride (23.8 g; 0.2 mol) in dichloromethane (120 ml) was added dropwise to the initial charge, which was kept under reflux. The reaction mixture was stirred under reflux for a further 2 h. The solution was cooled to room temperature, washed with H_2O (2 × 250 ml), dried over Na_2SO_4 and concentrated. The oily residue (6) was purified by column chromatography (Al_2O_3, CH_2Cl_2).

^{1}H-NMR ($CDCl_3$): δ (ppm) 2.46 (s, 3H, CH_3), 4.5 (s, 2H, CH_2), 7.2-7.3 (q, 4H, 4-MeS-Ph)

Example 3

1-Chloromethyl-4-methanesulfinylbenzene (3)

A solution of **2** (17.3 g; 0.1 mol) in glacial acetic acid (150 ml) was cooled to 10°C. A solution of H_2O_2 (35% strength solution; 13.1 g; 0.13 mol) in glacial acetic acid (50 ml) was added dropwise to the initial charge. The reaction mixture was stirred at room temperature for 2 h. The mixture was cooled in an ice bath, ice (200 g) was added and the mixture was neutralized with ammonia water (290 ml). The aqueous phase was extracted with ethyl acetate (2 × 300 ml). The organic phase was washed with H_2O (2 × 300 ml), dried over Na_2SO_4 and concentrated. By scratching and cooling the oily residue, **3** was obtained in crystalline form.

^{1}H-NMR ($CDCl_3$): δ (ppm) 2.73 (s, 3H, CH_3), 4.6 (s, 2H, CH_2), 7.5 (d, 2H, 4-MeS(O)-Ph), 7.6 (d, 2H, 4-MeS(O)-Ph)

Example 4

1-Chloromethyl-4-methanesulfonylbenzene (4)

m-Chloroperbenzoic acid (70%; 8.6 g; 0.04 mol) was introduced into a solution of **3** (3.0 g; 0.02 mol) in chloroform (50 ml). The reaction mixture was stirred under reflux for 4 h. The mixture was cooled to room temperature and filtered. The filtrate was washed with saturated $NaHCO_3$ solution (2 ×) and dried over Na_2SO_4. After concentration of the organic phase, **8** remained as a crystalline white solid. M.p. 102°C

^{1}H-NMR ($CDCl_3$): d (ppm) 3.07 (s, 3H, CH_3), 4.6 (s, 2H, CH_2), 7.6 (d, 2H, 4-$MeSO_2$-Ph), 7.9 (d, 2H, 4-$MeSO_2$-Ph)

Example 5

Methyl 5-chlorosulfonyl-2-hydroxybenzoate (5a)

5a was prepared from methyl salicylate (10.0 g; 65.7 mmol) using the method described in the synthesis of **5c**.

^{1}H-NMR ($CDCl_3$): δ (ppm) 4.05 (s, 3H, CH_3), 7.18 (d, 1H, 8.9 Hz, C^3-H), 8.09 (dd, 1H, 2.5/9.0 Hz, C^4-H), 8.57 (d, 1H, 2.5 Hz, C^6-H), 11.55 (s, 1H, exchangeable, phenol-OH)

Methyl 5-chloro-3-chlorosulfonyl-2-hydroxybenzoate (5b)

5b was prepared from methyl 5-chlorosalicylate (16.0 g; 85.7 mmol) using the method described in the synthesis of **5c**.

^{1}H-NMR ($CDCl_3$): δ (ppm) 4.06 (s, 3H, CH_3), 8.11 (d, 1H, 2.7 Hz, C^6-H), 8.19 (d,1H, 2.7 Hz, C^4-H), 12.09 (s, 1H, exchangeable, phenol-OH)

Ethyl 3-chlorosulfonyl-4-methoxybenzoate (5c)

A solution of ethyl 4-methoxybenzoate (15.7 g; 87.2 mmol) in CCl_4 (60 ml) was cooled to –15°C, and chlorosulfonic acid (17.5 ml; 263 mmol) was added dropwise over a period of 15 min, resulting in a temperature increase to –10°C. After the addition had ended, the reaction mixture was stirred at room temperature for 2 h and then heated at 50°C until no more starting material could be detected by thin-layer chromatography. With ice-cooling and vigorous stirring, the reaction mixture was added to a suspension of ice (50 g) in CCl_4 (100 ml). The mixture was stirred vigorously for 3 min. The organic phase was separated off and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 ml). The combined organic extracts were washed with saturated NaCl solution (3 ×), dried over Na_2SO_4 and concentrated. Trituration of the oily brown residue with diethyl ether resulted in **5c** precipitating as a crystalline white solid.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.41 (t, 3H, 7.1 Hz, CH_3), 4.14 (s, 3H, CH_3), 4.42 (q, 2H, 7.1Hz, CH_2), 7.18 (d, 1H, 8.8 Hz, C^5-H), 8.37 (dd, 1H, 2.1/8.8 Hz, C^6-H), 8.63 (d, 1H, 2.1 Hz, C^2-H)

Example 6

2-Hydroxy-5-mercaptobenzoic acid (6a)

6a was prepared from **6a** (0.50 g; 2.0 mmol) using the method described in the synthesis of **7c**, without alkylation with dimethyl sulfate.

^{1}H-NMR (DMSO-d_6): δ (ppm) 5.39 (bs, 1H, exchangeable, carboxyl-OH), 6.90 (d, 1H, 8.7 Hz, C^3-H), 7.45 (dd, 1H, 2.5/8.6 Hz, C^4-H), 7.75 (d,1H, 2.5 Hz, C^6-H), phenol-OH not visible

Example 7

2-Hydroxy-5-methylsulfanylbenzoic acid (7a)

7a was prepared from **5a** (10.0 g; 40.0 mmol) using the method described in the synthesis of **7c**.

^{1}H-NMR ($CDCl_3$): δ (ppm) 2.48 (s, 3H, CH_3), 6.97 (d, 1H, 8.7 Hz, C^3-H), 7.51 (dd, 1H, 2.5/8.7 Hz, C^4-H), 6.97 (d, 1H, 8.7 Hz, C^3-H), 7.87 (d, 1H, 2.4 Hz, C^6-H), 10.26 (bs, 1H, phenol-OH), CO_2H not visible

5-Chloro-2-hydroxy-3-methylsulfanylbenzoic acid (7b)

7b was prepared from **5b** (13.0 g; 45.6 mmol) using the method described in the synthesis of **7c**.

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.47 (s, 3H, CH_3), 7.33 (d, 1H, 2.4 Hz, C^6-H), 7.52 (d, 1H, 2.4 Hz, C^4-H), phenol-OH and CO_2H not visible

4-Methoxy-3-methylsulfanylbenzoic acid (7c)

Triphenylphosphine (20.5 g; 78.2 mmol) was introduced a little at a time into a solution of **5c** (5.1 g; 18.3 mmol) in toluene (50 ml). The reaction mixture was stirred at room temperature for 4.5 h. The precipitate (triphenylphosphine oxide) was filtered off, and the yellow filtrate was extracted with 10% strength aqueous sodium hydroxide solution (4 ×). Dimethyl sulfate (2 ml) was added to the combined aqueous extract, and the reaction mixture was stirred at room temperature for 2 h. The precipitate obtained was dissolved by heating to reflux temperature. The clear solution was cooled and adjusted to pH 1 using 20% strength hydrochloric acid. The precipitate **(7c)** was filtered off, washed with H_2O and dried under reduced pressure over $CaCl_2$.

^{1}H-NMR (CD_3OD): δ (ppm) 2.43 (s, 3H, S-CH_3), 3.93 (s, 3H, O-CH_3), 6.98 (d, 1H, 8.4 Hz, C^5-H), 7.79-7.86 (m, 2H, C^2-/C^6-H)

4-Hydroxy-3-methylsulfanylbenzoic acid (7d)

A suspension of **7c** (0.5 g; 2.5 mmol) in glacial acetic acid/48% strength hydrobromic acid (1+1, 7 ml) was stirred under reflux for 6 h. The reaction mixture was cooled, added to H_2O (20 ml) and adjusted to pH 2 using 10% strength Na_2CO_3 solution. The aqueous solution was extracted with diethyl ether (4 × 20 ml). The combined organic extract was washed with saturated NaCl solution (2 ×), dried over Na_2SO_4 and concentrated. On standing at room temperature, the off-brown oily residue **(7d)** crystallized out. The crystals were triturated with H_2O, filtered off and dried.

^{1}H-NMR ($CDCl_3$): δ (ppm) 2.38 (s, 3H, CH_3), 7.05 (d, 1H, 8.5 Hz, C^5-H), 8.02 (dd, 1H, 2.2/8.5 Hz, C^6-H), 8.29 (d, 1H, 2.2 Hz, C^2-H), phenol-OH and CO_2H not visible

Example 8

2-Hydroxymethyl-4-methylsulfanylphenol (8a)

8a was prepared from **7a** (1.5 g; 8.1 mmol) using the method described in the synthesis of **8c**.

^{1}H-NMR ($CDCl_3$): δ ppm) 2.42 (s, 3H, CH_3), 4.79 (s, 2H, CH_2), 6.81 (d, 1H, 8.4 Hz, C^6-H), 7.01 (d, 1H, 2.1 Hz, C^3-H), 7.17 (dd, 1H, 2.3/8.4 Hz, C^3-H), OH not visible

4-Chloro-2-hydroxymethyl-6-methylsulfanylphenol (8b)

8b was prepared from **7b** (2.2 g; 10.1 mmol) using the method described in the synthesis of **8c**.

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.38 (s, 3H, CH_3), 4.52 (s, 2H, CH_2), 5.3-5.5 (bs, 1H, exchangeable, hydroxyl-OH), 7.03 (d, 1H, 2.6 Hz, C^5-H), 7.11 (d, 2.4 Hz, C^3-H), 9.02 (bs, 1H, exchangeable, phenol-OH)

4-Hydroxymethyl-2-methylsulfanylphenol (8c)

With ice-cooling, a solution of **7d** (1.37 g; 7.4 mmol) in abs. tetrahydrofuran (THF; 15 ml) was added to a suspension of 95% pure $LiAlH_4$ (0.55 g; 14 mmol) in absolute THF (10 ml) in a three-necked flask (which had been dried by heating and flushed with argon) such that there was only a moderate evolution of gas. After the addition had ended, cooling was removed and the reaction mixture was stirred at room temperature for 30 min and at 55 – 65°C for a further 21 h. With ice-cooling, ice-water was added to the reaction mixture. The precipitate of $Al(OH)_3$ was dissolved by adding 10% strength sulfuric acid, and the aqueous-acidic solution (pH 1) was extracted with diethyl ether (3 × 50 ml). The combined ethereal extract was extracted with 10% strength aqueous sodium hydroxide solution (2 × 25 ml). The combined sodium hydroxide solution was neutralized with 20% strength hydrochloric acid. The precipitate **(8c)** was filtered off, washed with H_2O and dried. A further charge of **8c** was obtained by extraction of the neutral aqueous solution with diethyl ether. The ethereal extract was washed with saturated NaCl solution, dried over Na_2SO_4 and concentrated: crystalline white solid.

^{1}H-NMR ($CDCl_3$): δ (ppm) 2.34 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 6.97 (d, 1H, 8.3 Hz, C^6-H), 7.24 (dd, 1H, 2.0/8.4 Hz, C^5-H), 7.50 (d, 1H, 2.0 Hz, C^3-H), OH not visible

Example 9

2-Hydroxy-5-methylsulfanylbenzaldehyde (9a)

The title compound was obtained as a byproduct in the synthesis of **8a**.

^{1}H-NMR ($CDCl_3$): δ (ppm) 2.48 (s, 3H, CH_3), 6.96 (d, 1H, 9.8 Hz, C^3-H), 7.48-7.54 (m, 2H, C^4-/C^6-H), 9.87 (s, 1H, exchangeable, OH), 10.91 (s, 1H, aldehyde-H)

Example 10

4-(3-Chloroethyl)benzenesulfonyl chloride (10a)

With ice-cooling, (2-chloroethyl)benzene (14.0 g; 0.1 mol) was added dropwise over a period of 40 min to chlorosulfonic acid (72 g). The brown solution was stirred at room temperature for 24 h, cooled in an ice-bath and, a little at a time, added to ice, where a viscous material separated out that could not be filtered. The aqueous solution was extracted with ethyl acetate (3 ×). The combined organic extract was washed with 10% strength $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated. The oily residue was taken up in tert-butyl methyl ether/petroleum ether. The solution was scratched with a glass rod and cooled. The white crystals were filtered off and dried. Further reaction product was obtained from the mother liquor. The crude product was used without further purification for the synthesis of **11a**.

^{1}H-NMR ($CDCl_3$): δ (ppm) 3.20 (t, 2H, 6.8 Hz, CH_2), 3.79 (t, 2H, 6.8 Hz, CH_2), 7.46-7.53 (m, 2H, phenyl), 7.97-8.04 (m, 2H, phenyl)

4-(3-Chloropropyl)benzenesulfonyl chloride (10b)

10b was prepared from (3-chloropropyl)benzene (15.5 g; 0.1 mol) using the method described in the synthesis of **10a**. The crude product was used without further purification for the synthesis of **11b**.

MS: m/z (%) 253 (90. M^+), 217 (100. M^+-Cl), 189 (35), 153 (97, M^+-SO_2Cl), 125 (94), 119 (65, phenylpropylcarbenium$^+$), 91(90), 77 (29, phenyl$^+$)

Example 11

1-(3-Chloroethyl)-4-methylsulfanylbenzene (11a)

11a was prepared from **10a** (12.0 g; 0.05 mol) using the method described in the synthesis of **11b**.

^{1}H-NMR ($CDCl_3$): δ (ppm) 2.47 (s, 3H, CH_3), 3.02 (t, 2H, 7.4 Hz, CH_2), 3.68 (t, 2H, 7.5 Hz, CH_2), 7.11-7.25 (m, 4H, phenyl)

1-(3-Chloropropyl)-4-methylsulfanylbenzene (11b)

At room temperature, a solution of **10b** (12.7 g; 5.0 mmol) in diethyl ether (75 ml) was added dropwise over a period of 2.5 h to a suspension of $LiAlH_4$ (2.9 g; 7.6 mmol) in diethyl ether (50 ml). After the addition had ended, the reaction mixture was stirred at room temperature and with occasional addition of $LiAlH_4$ until no more starting material could be detected by thin-layer chromatography (2.5 h). With ice-cooling, ice was introduced into the reaction mixture, and the aqueous phase was acidified with 10% hydrochloric acid (pH 1). The organic phase was removed and the aqueous phase was extracted with diethyl ether (3 ×). The combined organic extract was washed with 10% strength aqueous sodium hydroxide solution (4 × 50 ml) until it was virtually colorless. Dimethyl sulfate (9.0 g; 7.0 mmol) was added to the combined sodium hydroxide extract, and the mixture was stirred at room temperature for 16.5 h. The oily sediment was taken up in diethyl ether. The organic phase was separated off and the aqueous phase was again extracted with diethyl ether (2 ×). The combined organic extract was dried over Na_2SO_4 and concentrated. The brown oily residue was subjected to a kugelrohr distillation (0.2 mbar, 250°C).

^{1}H-NMR ($CDCl_3$): δ (ppm) 2.01-2.11 (m, 2H, CH_2), 2.46 (s, 3H, CH_3), 2.73 (t, 2H, 7.1 Hz, CH_2), 3.51 (t, 2H, 6.5 Hz, CH_2), 7.09-7.25 (m, 4H, phenyl)

Example 12

1-(2-Chloroethyl)-4-methanesulfinylbenzene (12a)

With cooling, a 35% strength solution of H_2O_2 (0.9 g; 9.3 mmol) was added to a solution of **11a** (1.5 g; 8.0 mmol) in glacial acetic acid (20 ml). After the addition had ended, the reaction mixture was stirred at room temperature for 2.5 h diluted with cooling with ice-water and adjusted to pH 8 using 25% strength ammonia water. The oily white sediment was taken up in diethyl ether and the aqueous phase was ex-

tracted with diethyl ether (3 ×). The combined organic extract was dried over Na_2SO_4 and concentrated.

^{1}H-NMR ($CDCl_3$): δ (ppm) 2.73 (s, 3H, CH_3), 3.14 (t, 2H, 7.1 Hz, CH_2), 3.76 (t, 2H, 7.1 Hz, CH_2), 7.38-7.42 (m, 2H, phenyl), 7.60-7.64 (m, 2H, phenyl)

1-(3-Chloropropyl)-4-methanesulfinylbenzene (12b)

12b was prepared from **11b** (2.0 g; 10.0 mmol) using the method described in the synthesis of **12a**. M.p.: 46°C

General methods for preparing the compounds of the formula I:

Preparation of the 2-arylalkyl- or alkylsulfanylimidazoles (general method A)

A suspension of the respective imidazole-2-thione (1 equivalent), of the respective base (1.2 equivalents) and of the respective arylalkyl or alkyl halide (1 equivalent) in ethanol/THF (8+2) was stirred under reflux until no more imidazole-2-thione could be detected by thin-layer chromatography. The reaction mixture was cooled to room temperature and filtered. The filtrate, which in most cases was of red/orange color, was concentrated, and the residue was purified by column chromatography, recrystallization or trituration. The compounds **13a - c, 14a - c** and **17a - m** were prepared in this manner.

Preparation of the 2-benzylsulfanylimidazoles having phenolic functionality in the radical R^2 (general method B)

By addition of 10% strength hydrochloric acid (10 - 15 drops), the imidazole-2-thione **1a** (1 equivalent) was dissolved in glacial acetic acid (5 ml). The respective benzyl alcohol (1 equivalent) was added to the initial charge, which had a light-yellow color, and the reaction mixture was stirred at a suitable temperature (temperature/time) until no more **1a** could be detected by thin-layer chromatography. In the case of the sulfoxides **18g-i**, a 35% strength solution of H_2O_2 was added, and the reaction mixture was stirred at room temperature for a further 4 h. The reaction mixture was diluted

with H_2O (5 ml) and adjusted to pH 8 using 25% strength ammonia water. The precipitate was filtered off and washed with water. The crude product was purified by column chromatography, recrystallization or trituration. The imidazol-2-ylsulfanylmethylphenols **18a-i** were prepared in this manner.

Preparation of N-substituted 2-aminopyridines (general method C)

Under argon, the respective 5-(2-halopyridin-4-yl)imidazole (1 equivalent) was suspended in the respective amine (about 10 equivalents). The reaction mixture was stirred at the respective temperature until no more starting material could be detected by thin-layer chromatography. The reaction mixture was cooled to room temperature and taken up in 10% citric acid which had been adjusted beforehand to pH 5 using 20% strength NaOH. The aqueous emulsion was extracted with ethyl acetate (3 ×). The combined organic extract was washed with 10% strength citric acid/pH 5 (1 ×), 10% strength Na_2CO_3 solution (2 ×) and saturated NaCl solution (1 ×), dried over Na_2SO_4 and concentrated. The oily residue was separated by column chromatography. The aminopyridines **25f-p, 26c-e** and **27c-d** were prepared in this manner.

Example 13

3-[5-(4-Fluorophenyl)-2-(4-methylsulfanylbenzylsulfanyl)-3H-imidazol-4-yl]-pyridine (13a)

Using the general method A, the title compound was obtained from **1b** (0.42 g; 1.5 mmol) and **2** (0.25 g; 1.4 mmol) after a reaction time of 4.5 hours and separation by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1).
M.p. 163°C

IR (ATR) (attenuated total reflection) 1506, 1493, 1222 (C-F), 837, 806 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.45 (s, 3H, CH_3), 4.38 (s, 2H, CH_2), 7.19-7.49 (m, 10H, 3-Pyr, 4-F-Ph and 4-MeS-Ph), 7.78-7.82 (m, 1H, 3-Pyr), 8.45-8.47 (m, 1H, 3-Pyr), 8.61 (s, 1H, 3-Pyr), 12.71 (bs, 1H, exchangeable, NH)

3-[5-(4-Fluorophenyl)-2-(4-methanesulfinylbenzylsulfanyl)-3H-imidazol-4-yl]-pyridine (13b).

Using the general method A, the title compound was obtained from **1b** (0.42 g; 1.5 mmol) and **3** (0.27 g; 1.5 mmol) after a reaction time of 8 hours and separation by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1).
M.p. 127°C

IR (ATR): 1506, 1222 (C-F), 1027 (S=O), 1013, 838, 811 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 3.19 (s, 3H, CH_3), 4.46 (s, 2H, CH_2), 7.16-7.46 (m, 5H, 3-Pyr and 4-F-Ph), 7.56-7.66 (m, 4H, 4-MeS(O)-Ph), 7.72-7.81 (m, 1H, 3-Pyr), 8.41-8.62 (m, 2H, 3-Pyr), 12.77 (bs, 1H, exchangeable, NH)

3-[5-(4-Fluorophenyl)-2-(4-methanesulfonylbenzylsulfanyl)-3H-imidazol-4-yl]-pyridine (13c).

Using the general method A, the title compound was obtained from **1b** (0.42 g; 1.5 mmol) and **4** (0.29 g; 1.43 mmol) and with addition of Na_2CO_3 (0.43 g; 4.1 mmol) after a reaction time of 6.5 hours and trituration with hot ethyl acetate. M.p. 129°C

IR (ATR): 1506, 1296 (SO2), 1222 (C-F), 1145 (SO2), 1089, 839, 812 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 3.19 (s, 3H, CH_3), 4.50 (s, 2H, CH_2), 7.17-7.45 (m, 5H, 3-Pyr and 4-F-Ph), 7.64-7.90 (m, 5H, 3-Pyr and 4-MeSO_2-Ph), 8.43-8.61 (m, 2H, 3-Pyr), 12.78 (bs, 1H, exchangeable, NH)

Example 14

4-[5-(4-Chlorophenyl)-2-(4-methylsulfanylbenzylsulfanyl)-3H-imidazol-4-yl]-pyridine (14a)

Using the general method A, the title compound was obtained from **1c** (0.26 g; 0.9 mmol) and **6** (0.15 g; 0.87 mmol) and with addition of Na_2CO_3 (two spatula tips) after a reaction time of 6.5 hours and separation by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1). M.p. 236°C

IR (ATR): 1600, 1492, 1094, 1005, 968, 829, 684 (C-Cl), 561 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.44 (s, 3H, CH_3), 4.38 (s, 2H, CH_2), 7.18-7.56 (m, 10H, 4-Pyr, 4-Cl-Ph and 4-MeS-Ph), 8.45-8.55 (m, 2H, 4-Pyr), 12.86 (bs, 1H, exchangeable, NH)

4-[5-(4-Chlorophenyl)-2-(4-methanesulfinylbenzylsulfanyl)-3H-imidazol-4-yl]-pyridine (14b)

Using the general method A, the title compound was obtained from **1c** (0.26 g; 0.9 mmol) and **3** (0.16 g; 0.85 mmol) and with addition of a reaction time of 6.5 hours and separation by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1). M.p. 224°C

IR (ATR): 1600, 1510, 1490, 1033 (S=O), 1001, 967, 829, 677 cm^{-1} (C-Cl)

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.70 (s, 3H, CH_3), 4.47 (s, 2H, CH_2), 7.31-7.65 (m, 10H, 4-Pyr, 4-Cl-Ph and 4-MeS(O)-Ph), 8.44-8.54 (m, 2H, 4-Pyr), 12.87 (bs, 1H, exchangeable, NH)

4-[5-(4-Chlorophenyl)-2-(4-methanesulfonylbenzylsulfanyl)-3H-imidazol-4-yl]-pyridine (14c)

Using the general method A, the title compound was obtained from **1c** (0.26 g; 0.9 mmol) and **4** (0.18 g; 0.9 mmol) and with addition of Na_2CO_3 (two spatula tips) after a reaction time of 6.5 hours and separation by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1). M.p. 232°C

IR (ATR): 1603, 1490, 1300 (SO2), 1141 (SO2), 1086, 1002, 952, 829, 681 (C-Cl), 550 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 3.19 (s, 3H, CH_3), 4.52 (s, 2H, CH_2), 7.32-7.58 (m, 6H, 4-Pyr and 4-Cl-Ph), 7.67 (d, 2H, 8.2 Hz, 4-$MeSO_2$-Ph), 7.88 (d, 2H, 8.3 Hz, 4-$MeSO_2$-Ph), 8.45-8.55 (m, 2H, 4-Pyr), 12.89 (bs, 1H, exchangeable, NH)

Example 15

4-[5-(4-Bromophenyl)-2-(4-methylsulfanylbenzylsulfanyl)-3H-imidazol-4-yl]-pyridine (15a)

Using the general method A, the title compound was obtained from **1d** (0.25 g; 0.75 mmol) and **2** (0.13 g; 0.72 mmol) after a reaction time of 5 hours and separation by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1).

IR (ATR): 1600, 1517, 1490, 1089, 1069, 1003, 968, 826 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.43 (s, 3H, CH_3), 4.36 (s, 2H, CH_2), 7.16-7.87 (m, 10H, 4-Pyr, 4-Br-Ph and 4-MeS-Ph), 8.45-8.55 (m, 2H, 4-Pyr), 12.90 (bs, 1H, exchangeable, NH)

4-[5-(4-Bromophenyl)-2-(4-methanesulfinylbenzylsulfanyl)-3H-imidazol-4-yl]-pyridine (15b)

Using the general method A, the title compound was obtained from **1d** (0.25 g; 0.75 mmol) and **3** (0.14 g; 0.72 mmol) after a reaction time of 10 hours and separation by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1).
M.p. 222°C

IR (ATR): 1604, 1487, 1035 (S=O), 1010, 1000, 966, 822 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.71 (s, 3H, CH_3), 4.48 (s, 2H, CH_2), 7.40-7.62 (m, 20H, 4-Pyr, 4-Br-Ph and 4-MeS(O)-Ph), 8.49-8.57 (m, 2H, 4-Pyr), 12.90 (bs, 1H, exchangeable, NH)

4-[5-(4-Bromophenyl)-2-(4-methanesulfonylbenzylsulfanyl)-3H-imidazol-4-yl]-pyridine (15c)

Using the general method A, the title compound was obtained from **1d** (0.25 g; 0.75 mmol) and **4** (0.15 g; 0.72 mmol) after a reaction time of 5 hours and separation by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1).
M.p. 226°C

IR (ATR): 1605, 1318, 1303 (SO2), 1145 (SO2), 1003, 967, 957, 827, 822 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 3.18 (s, 3H, CH_3), 4.50 (s, 2H, CH_2), 7.33-7.89 (m, 10H, 4-Pyr, 4-Br-Ph and 4-MeSO_2-Ph), 8.45-8.54 (m, 2H, 4-Pyr), 12.91 (bs, 1H, exchangeable, NH)

Example 16

4-[2-(4-Methylsulfanylbenzylsulfanyl)-5-phenyl-3H-imidazol-4-yl]pyridine (16a)

Using the general method A, the title compound was obtained from **1e** (0.38 g; 1.5 mmol) and **2** (0.25 g; 1.4 mmol) after a reaction time of 5.75 hours and separation by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1).
M.p. 213°C

IR (ATR): 1601, 1491, 1417, 1094, 1004, 967, 828, 771, 700 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.44 (s, 3H, CH_3), 4.38 (s, 2H, CH_2), 7.18-7.58 (m, 11H, 4-Pyr, Ph and 4-MeS-Ph), 8.44-8.47 (m, 2H, 4-Pyr), 12.82 (bs, 1H, exchangeable, NH)

4-[2-(4-Methanesulfinylbenzylsulfanyl)-5-phenyl-3H-imidazol-4-yl]pyridine (16b)

Using the general method A, the title compound was obtained from **1e** (0.38 g; 1.5 mmol) and **3** (0.27 g; 1.43 mmol) after a reaction time of 5.5 hours and separation by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1).
M.p. 189°C

IR (ATR): 1603, 1494, 1051 (S=O), 1003, 833, 701 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.71 (s, 3H, CH_3), 4.48 (s, 2H, CH_2), 7.32-7.52 (m, 7H, 4-Pyr and Ph), 7.57-7.67 (m, 4H, 4-MeS(O)-Ph), 8.45-8.54 (m, 2H, 4-Pyr), 12.84 (bs, 1H, exchangeable, NH)

4-[2-(4-Methanesulfonylbenzylsulfanyl)-5-phenyl-3H-imidazol-4-yl]pyridine (16c)

Using the general method A, the title compound was obtained from **1e** (0.38 g; 1.5 mmol) and **4** (0.29 g; 1.43 mmol) after a reaction time of 4.25 hours and separation by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1).
M.p. 247°C

IR (ATR): 1602, 1298 (SO2), 1145 (SO2), 1006, 953, 827, 775, 701 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 3.21 (s, 3H, CH_3), 4.54 (s, 2H, CH_2), 7.31-7.58 (m, 7H, 4-Pyr and Ph), 7.70 (d, 2H, 8.3 Hz, 4-MeSO_2-Ph), 7.91 (d, 2H, 8.3 Hz, 4-MeSO_2-Ph), 8.45-8.59 (m, 2H, 4-Pyr), 12.87 (bs, 1H, exchangeable, NH)

Example 17

4-{5-(4-Fluorophenyl)-2-[2-(4-methanesulfinylphenyl)ethylsulfanyl]-1H-imidazol-4-yl}pyridine (17a)

Using the general method A, the title compound was obtained from **1a** (0.25 g; 0.9 mmol) and **12a** (0.22 g; 1.1 mmol) and with addition of Na_2CO_3 (1 spatula tip) and a catalytic amount of NaI after a reaction time of 50 hours and purification by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1).
M.p. 177°C

IR (ATR): 1221 (C-F), 1032 cm^{-1} (S=O)

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.71 (s, 3H, CH_3), 3.06-3.13 (m, 2H, CH_2), 3.42-3.49 (m, 2H, CH_2), 7.25-7.65 (m, 10H, 4-Pyr, 4-F-Ph and 4-MeS(O)-Ph), 8.40-8.58 (m, 2H, 4-Pyr), 12.80 (bs, 1H, exchangeable, NH)

4-{5-(4-Fluorophenyl)-2-[2-(4-methanesulfinylphenyl)propylsulfanyl]-1H-imidazol-4-yl}pyridine (17b)

Using the general method A, the title compound was obtained from **1a** (0.25 g; 0.9 mmol) and **12b** (0.22 g; 1.0 mmol) and with addition of Na_2CO_3 (1 spatula tip) and a catalytic amount of NaI after a reaction time of 40 hours and purification by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1).
M.p. 142°C

IR (ATR): 1222 (C-F), 1043 cm^{-1} (S=O)

^{1}H-NMR (DMSO-d_6): δ (ppm) 1.95-2.09 (m, 2H, CH_2), 2.71 (s, 3H, CH_3), 2.82 (t, 2H, 7.4 Hz, CH_2), 3.15 (t, 2H, 7.0 Hz, CH_2), 7.25-7.62 (m, 10H, 4-Pyr, 4-F-Ph and 4-MeS(O)-Ph), 8.46-8.49 (m, 2H, 4-Pyr), 12.86 (bs, 1H, exchangeable, NH)

4-[2-Benzylsulfanyl-5-(4-fluorophenyl)-1H-imidazol-4-yl]pyridine (17c)

Using the general method A, the title compound was obtained from **1a** (0.28 g; 1.0 mmol) and 1-chloromethylbenzene (0.13 g; 1.0 mmol) after a reaction time of 6 hours and trituration with MeOH. M.p. 223°C

IR (ATR): 1233 cm^{-1} (C-F)

^{1}H-NMR (DMSO-d_6): δ (ppm) 4.41 (s, 2H, CH_2), 7.23-7.51 (m, 11H, 4-Pyr, 4-F-Ph and Bz), 8.44-8.47 (m, 2H, 4-Pyr), 12.82 (bs, 1H, exchangeable, NH)

4-[5-(4-Fluorophenyl)-2-phenethylsulfanyl-1H-imidazol-4-yl]pyridine (17d)

Using the general method A, the title compound was obtained from **1a** (0.5 g; 1,9 mmol) and 2-chloroethylbenzene (0.28 g; 2.0 mmol) and with addition of Na_2CO_3 (1 spatula tip) and a catalytic amount of NaI after a reaction time of 70 hours and trituration with EtOH. M.p. 257°C

IR (ATR): 1223 cm^{-1} (C-F)

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.99 (t, 2H, 7.4 Hz, CH_2), 3.40 (t, 2H, 7.5 Hz, CH_2), 7.17-7.53 (m, 11H, 4-Pyr, 4-F-Ph and Bz), 8.44-8.46 (m, 2H, 4-Pyr), NH not visible

4-[5-(4-Fluorophenyl)-2-(3-phenylpropylsulfanyl)-1H-imidazol-4-yl]pyridine (17e)

Using the general method A, the title compound was obtained from **1a** (0.5 g; 1,9 mmol) and 3-chloropropylbenzene (0.31 g; 2.0 mmol) and with addition of Na_2CO_3 (1 spatula tip) and a catalytic amount of NaI after a reaction time of 70 hours and trituration with EtOH. M.p. 183°C

IR (ATR): 1226 cm^{-1} (C-F)

^{1}H-NMR (DMSO-d_6): δ (ppm) 1.90-2.04 (m, 2H, CH_2), 2.72 (t, 2H, 7.4 Hz, CH_2), 3.12 (t, 2H, 7.0 Hz, CH_2), 7.18-7.51 (m, 11H, 4-Pyr, 4-F-Ph and Bz), 8.37-8.44 (m, 2H, 4-Pyr), 12.82 (bs, 1H, exchangeable, NH)

[5-(4-Fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-ylsulfanyl]acetonitrile (17f)

Using the general method A, the title compound was obtained from **1a** (1.1 g; 4.0 mmol) and chloroacetonitrile (0.30; 4.0 mmol) after a reaction time of 18 hours and purification by column chromatography (SiO_2 60, ethyl acetate).
M.p. 219°C

IR (ATR): 2243 (CN), 1226 cm^{-1} (C-F)

^{1}H-NMR (DMSO-d_6): δ (ppm) 4.32 (s, 2H, CH_2), 7.34-7.57 (m, 6H, 4-Pyr and 4-F-Ph), 8.50-8.52 (m, 2H, 4-Pyr), 13.20 (bs, 1H, exchangeable, NH)

4-[5-(4-Fluorophenyl)-2-(naphthalen-1-ylmethylsulfanyl)-1H-imidazol-4-yl]-pyridine (17g)

Using the general method A, the title compound was obtained from **1a** (0.28 g; 1.0 mmol) and 1-chloromethylnaphthol (0.18 g; 1.0 mmol) after a reaction time of 6.5 hours and purification by column chromatography (SiO_2 60, ethyl acetate). M.p. 364°C

IR (ATR): 1225 cm^{-1} (C-F)

^{1}H-NMR (DMSO-d_6): δ (ppm) 4.90 (s, 2H, CH_2), 7.25-7.62 (m, 10H, 4-Pyr, 4-F-Ph and naphthyl), 7.80-7.98 (m, 2H, naphthyl), 8.20-8.23 (m, 1H, naphthyl), 8.48-8.52 (m, 2H, 4-Pyr), 12, (bs, 1H, exchangeable, NH)

4-[2-cyclohexylmethylsulfanyl-5-(4-fluorophenyl)-1H-imidazol-4-yl]pyridine (17h)

Using the general method A, the title compound was obtained from **1a** (0.25 g; 0.9 mmol) and 1-chloromethylcyclohexane (0.18 g; 1.0 mmol) and with addition of Na_2CO_3 (1 spatula tip) and a catalytic amount of NaI after a reaction time of 47 hours and trituration with EtOH. M.p. 235°C

IR (ATR): 2922, 2852 (c-Hex), 1222 cm^{-1} (C-F)

^{1}H-NMR (DMSO-d_6): δ (ppm) 0.95-1.23 (m, 5H, *cyclo*-Hex), 1.51-1.85 (m, 6H, *cyclo*-Hex), 3.06 (d, 2H, 6.7 Hz, CH_2), 7.22-7.51 (m, 6H, 4-Pyr and 4-F-Ph), 8.43-8.45 (m, 2H, 4-Pyr), 12.76 (bs, 1H, exchangeable, NH)

4-[5-(4-Fluorophenyl)-2-methylsulfanyl-1H-imidazol-4-yl]pyridine (17i)

Using the general method A, the title compound was obtained from **1a** (0.41 g; 1.5 mmol) and methyl iodide (0.27 g; 1.9 mmol) after a reaction time of 8 hours and trituration with EtOH. M.p. 263°C

IR (ATR): 1226 cm^{-1} (C-F)

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.61 (s, 3H, CH_3), 7.22-7.51 (m, 6H, 4-Pyr and 4-F-Ph), 8.42-8.45 (m, 2H, 4-Pyr), NH not visible

4-[5-(4-Fluorophenyl)-2-(2-methylsulfanylbenzylsulfanyl)-1H-imidazol-4-yl]-pyridine (17j)

Using the general method A, the title compound was obtained from **1a** (0.28 g; 1.0 mmol) and 1-chloromethyl-2-methylsulfanylbenzene (0.17 g; 1.0 mmol) after a reaction time of 5.5 hours and purification by column chromatography (SiO_2 60, ethyl acetate). M.p. 223°C

IR (ATR): 1228 cm^{-1} (C-F)

^{1}H-NMR (CD_3OD): δ (ppm) 2.51 (s, 3H, CH_3), 4.44 (s, 2H, CH_2), 7.13-7.48 (m, 10H, 4-Pyr, 4-F-Ph and 2-MeS-Ph), 8.43-8.46 (m, 2H, 4-Pyr)

4-[5-(4-Fluorophenyl)-2-(2-methanesulfinylbenzylsulfanyl)-1H-imidazol-4-yl]-pyridine (17k)

Using the general method A, the title compound was obtained from **1a** (0.28 g; 1.0 mmol) and 1-chloromethyl-2-methanesulfinylbenzene (0.18 g; 1.0 mmol) after a reaction time of 4 hours and recrystallization from methanol/ethyl acetate (1+1). M.p. 205°C

IR (KBr): 1213 (C-F), 1033 cm^{-1} (S=O)

^{1}H-NMR (CD_3OD): δ (ppm) 2.87 (s, 3H, CH_3), 4.50 (d, 1H, 13.6 Hz, CH_2), 4.62 (d, 1H, 13.6 Hz, CH_2), 7.24-7.33 (m, 2H, 4-F-Ph), 7.47-7.62 (m, 5H, 4-F-Ph, C^4-/C^5-/C^6-H 2-MeS(O)-Ph), 7.95 (d, 1H, 7.2 Hz, C^3-H 2-MeS(O)-Ph), 7.99-8.03 (m, 2H, 4-Pyr), 8.55-8.58 (m, 2H, 4-Pyr)

4-[5-(4-Fluorophenyl)-2-(3-methylsulfanylbenzylsulfanyl)-1H-imidazol-4-yl]-pyridine (17l)

Using the general method A, the title compound was obtained from **1a** (1.1 g; 4.1 mmol) and 1-chloromethyl-3-methylsulfanylbenzene (0.7 g; 4.1 mmol) after a reaction time of 11 hours and recrystallization from EtOH. M.p. 218°C

IR (KBr): 1225 cm^{-1} (C-F)

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.40 (s, 3H, CH_3), 4.46 (s, 2H, CH_2), 7.16-7.43 (m, 6H, 4-F-Ph and 3-MeS-Ph), 7.56-7.63 (m, 2H, 4-F-Ph), 7.90-7.93 (m, 2H, 4-Pyr), 8.66-8.69 (m, 2H, 4-Pyr), NH not visible

4-[5-(4-Fluorophenyl)-2-(3-methanesulfinylbenzylsulfanyl)-1H-imidazol-4-yl]-pyridine (17m)

A 35% strength solution of H_2O_2 (0.13 ml; 1.3 mmol) was added dropwise to a suspension of **17l** (0.50 g; 1.2 mmol) in glacial acetic acid (7 ml). The reaction mixture was stirred at room temperature for 20.5 h, diluted with H_2O (5 ml), adjusted to pH 9 using 25% strength ammonia water and extracted with ethyl acetate (3 ×). The combined organic extract was washed with saturated NaCl solution (3 ×) and dried over Na_2SO_4. The oily crude product obtained after removal of the solvent was triturated with diethyl ether/ethyl acetate (1+1) and the semi-solid residue was purified by column chromatography (RP-18, MeOH). M.p. 171°C

IR (KBr): 1228 (C-F), 1019 cm^{-1} (S=O)

^{1}H-NMR (CD_3OD): δ (ppm) 2.67 (s, 3H, CH_3), 4.37 (s, 2H, CH_2), 7.13-7.21 (m, 2H, 4-F-Ph), 7.37-7.58 (m, 8H, 4-Pyr, 4-F-Ph and 3-MeS(O)-Ph), 8.40-8.43 (m, 2H, 4-Pyr)

Example 18

2-[5-(4-Fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-ylsulfanylmethyl]phenol (18a)

Using the general method B (23 h, room temperature), the title compound was obtained from **1a** (0.20 g; 0.7 mmol) and 2-hydroxymethylphenol (0.10 g; 0.8 mmol) after trituration with EtOH. M.p. 200°C (decomposition)

IR (ATR): 1266 (OH bending), 1222 (C-F), 1005 (C-O)

^{1}H-NMR (DMSO-d_6): δ (ppm) 4.37 (s, 2H, CH_2), 6.70-6.85 (m, 2H, 2-HO-Ph), 7.05-7.14 (m, 1H, 2-HO-Ph), 7.23-7.53 (m, 7H, 4-Pyr, 4-F-Ph and 2-HO-Ph), 8.46-8.49 (m, 2H, 4-Pyr), 9.95 (bs, 1H, exchangeable, OH), 12.81 (bs, 1H, exchangeable, NH)

3-[5-(4-Fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-ylsulfanylmethyl]phenol (18b)

Using the general method B (9 h, reflux), the title compound was obtained from **1a** (0.20 g; 0.7 mmol) and 3-hydroxymethylphenol (0.10 g; 0.8 mmol) after purification by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1).
M.p. 230°C

IR (ATR): 1287 (OH bending), 1241 (C-F), 1007 cm^{-1} (C-O)

^{1}H-NMR (DMSO-d_6): δ (ppm) 4.34 (s, 2H, CH_2), 6.65 (dd, 1H, 1.4/8.0 Hz, 3-HO-Ph C^4-H), 6.79-6.82 (m, 2H, 3-HO-Ph C^2-/C^6-H), 7.07-7.15 (m, 1H, 3-HO-Ph C^5-H), 7.27-7.53 (m, 6H, 4-Pyr and 4-F-Ph), 9.45 (s, 1H, exchangeable, OH), 12.83 (bs, 1H, exchangeable, NH)

4-[5-(4-Fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-ylsulfanylmethyl]phenol (18c)

Using the general method B (14 h, room temperature), the title compound was obtained from **1a** (0.20 g; 0.7 mmol) and 4-hydroxymethylphenol (0.10 g; 0.8 mmol) after purification by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1).
M.p. 250°C (decomposition)

IR (ATR): 1271 (OH bending), 1232 (C-F), 1004 cm^{-1} (C-O)

^{1}H-NMR (DMSO-d_6): δ (ppm) 4.32 (s, 2H, CH_2), 6.69 (d, 2H, 7.5 Hz, 4-HO-Ph), 7.19 (d, 2H, 7.9 Hz, 4-HO-Ph), 7.27-7.51 (m, 6H, 4-Pyr and 4-F-Ph), 8.43-8.53 (m, 2H, 4-Pyr), 9.41 (s, 1H, exchangeable, OH), 12.79 (bs, 1H, exchangeable, NH)

2-[5-(4-Fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-ylsulfanylmethyl]-4-methylsulfanylphenol (18d)

Using the general method B (1 h, room temperature), the title compound was obtained from **1a** (0.50 g; 2.9 mmol) and **8a** (0.50 g; 2.9 mmol) after trituration with MeOH. M.p. 243°C

IR (KBr): 1275 (OH bending), 1230 (C-F), 1005 cm^{-1} (C-O)

^{1}H-NMR (DMF-d_7): δ (ppm) 2.36 (s, 3H, CH_3), 4.46 (s, 2H, CH_2), 6.90 (d, 1H, 8.4 Hz, 2-HO-Ph C^3-H), 7.13 (dd, 1H, 2.3/8.3 Hz, 2-HO-Ph C^4-H), 7.27-7.35 (m, 3H, 4-F-Ph and 2-HO-Ph C^6-H), 7.51-7.53 (m, 2H, 4-Pyr), 7.58-7.65 (m, 2H, 4-F-Ph), 8.52-8.55 (m, 2H, 4-Pyr), 10.30-10.70 (bs, 1H, exchangeable, NH), OH not visible

4-Chloro-2-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-ylsulfanylmethyl]-6-methylsulfanylphenol (18e)

Using the general method B (1.5 h, 75°C), the title compound was obtained from **1a** (0.80 g; 3.0 mmol) and **8b** (0.60 g; 3.0 mmol) after trituration with MeOH. M.p. 220°C (decomposition)

IR (KBr): 1259 (OH bending), 1225 (C-F), 1007 cm^{-1} (C-O)

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.34 (s, 3H, CH_3), 4.38 (s, 2H, CH_2), 6.97 (d, 1H, 2.3 Hz, 3-Cl-Ph C^2-H), 7.17 (d, 1H, 2.3 Hz, 3-Cl-Ph C^4-H), 7.23-7.51 (m, 6H, 4-Pyr and 4-F-Ph), 8.48-8.50 (m, 2H, 4-Pyr), 12.74 (bs, 1H, exchangeable, NH), OH not visible

4-[5-(4-Fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-ylsulfanylmethyl]-2-methylsulfanylphenol (18f)

Using the general method B (2 h, room temperature), the title compound was obtained from **1a** (0.20 g; 0.7 mmol) and **8c** (0.14 g, 0.8 mmol) after trituration with MeOH. M.p. 230°C (decomposition)

IR (KBr): 1227 (C-F), 1019 cm^{-1} (C-O)

^{1}H-NMR (CD_3OD): δ (ppm) 2.21 (s, 3H, CH_3), 4.17 (s, 2H, CH_2), 6.69 (d, 1H, 8.0 Hz, 4-HO-Ph C^3-H), 6.90-7.01 (m, 2H, 4-HO-Ph C^2-/C^6-H), 7.12-7.21 (m, 2H, 4-F-Ph), 7.32-7.53 (m, 4H, 4-Pyr and 4-F-Ph), 8.39-8.43 (m, 2H, 4-Pyr)

2-[5-(4-Fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-ylsulfanylmethyl]-4-methanesulfinylphenol (18g)

Using the general method B (1 h, room temperature), the title compound was obtained from **1a** (0.27 g; 1.0 mmol) and **8a** (0.17 g; 1.0 mmol) with addition of 35% strength H_2O_2 solution after recrystallization from toluene/THF (1+1). M.p. 216°C

IR (KBr): 1278 (OH bending), 1232 (C-F), 1031 (S=O), 1003 cm^{-1} (C-O)

^{1}H-NMR (CD_3OD): δ (ppm) 2.60 (s, 3H, CH_3), 4.33 (s, 2H, CH_2), 6.96 (d, 1H, 8.2 Hz, 2-HO-Ph C^3-H), 7.11-7.21 (m, 2H, 4-F-Ph), 7.41-7.47 (m, 6H, 4-Pyr, 4-F-Ph and 2-HO-Ph C^4-/C^6-H), 8.39-8.42 (m, 2H, 4-Pyr)

4-Chloro-2-[5-(4-fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-ylsulfanylmethyl]-6-methanesulfinylphenol (18h)

Using the general method B (1.5 h, 75°C), the title compound was obtained from **1a** (0.27 g; 1.0 mmol) and **8b** (0.21 g, 1.0 mmol) with addition of 35% strength H_2O_2 solution after purification by column chromatography (SiO_2 60, acetone). M.p. 175°C (decomposition)

IR (KBr): 1265 (OH bending), 1236 (C-F), 1051 (S=O), 1005 cm^{-1} (C-O)

^{1}H-NMR (CD_3OD): δ (ppm) 2.72 (s, 3H, CH_3), 4.39 (s, 2H, CH_2), 7.14-7.23 (m, 2H, 4-F-Ph), 7.39 (d, 1H, 2.6 Hz, 3-Cl-Ph C^2-H), 7.42-7.49 (m, 6H, 4-Pyr, 4-F-Ph and 3-Cl-Ph C^4-H), 8.43-8.46 (m, 2H, 4-Pyr)

4-[5-(4-Fluorophenyl)-4-pyridin-4-yl-1H-imidazol-2-ylsulfanylmethyl]-2-methanesulfinylphenol (18i)

Using the general method B (2.5 h, room temperature), the title compound was obtained from **1a** (0.20 g; 0.7 mmol) and **8c** (0.14 g; 0.8 mmol) with addition of 35% strength H_2O_2 solution after trituration with acetone.
M.p. 185°C (decomposition)

IR (KBr): 1296 (OH bending), 1230 (C-F), 1062 (S=O), 1013 cm^{-1} (C-O)

^{1}H-NMR (CD_3OD): δ (ppm) 2.70 (s, 3H, CH_3), 4.28 (s, 2H, CH_2), 6.78 (d, 1H, 8.3 Hz, 4-HO-Ph C^3-H), 7.12-7.21 (m, 2H, 4-F-Ph), 7.28 (dd, 1H, 2.2/8.3 Hz, 4-HO-Ph C^2-H), 7.39-7.46 (m, 5H, 4-Pyr, 4-F-Ph and 4-HO-Ph C^6-H), 8.40 (m, 2H, 4-Pyr)

Example 20

4-Fluoro-N-methoxy-N-methylbenzamide (20)

A suspension of 4-fluorobenzoic acid (20 g, 143 mmol) in thionyl chloride (130 g; 1.1 mol) was stirred under reflux for 6 h: vigorous evolution of gas, clear solution after about 10 min, deepening of the color from yellow to orange. Excess thionyl chloride was removed by distillation (initially atmospheric pressure/40°C, then membrane pump vacuum/40°C). From the distillation residue, 4-fluorobenzoyl chloride was distilled off under membrane pump vacuum at 90°C over a short column. The reaction product crystallized on storing in a fridge (n^{20}_D 1.5315; m.p. 9°C, yield 20 g/89%). Freshly distilled triethylamine (29 ml) was added to a suspension of N,O-dimethylhydroxylamine hydrochloride (9.0 g; 92 mmol) in CH_2Cl_2 (75 ml). The reaction mixture was stirred at room temperature for 2 h and then cooled to -10°C. With cooling, 4-fluorobenzoyl chloride (13.5 g; 85 mmol) was, over a period of 6 min, added dropwise to the initial charge. After the addition had ended, cooling was removed and the reaction mixture was stirred at room temperature for 1.5 h. The light-brown suspension was poured into H_2O (100 ml). The organic phase was removed and the aqueous phase was extracted with diethyl ether (2 ×). The combined extract

was washed with saturated NaCl solution, dried over $NaSO_4$ and concentrated. The oily brown residue crystallized on cooling and scratching. The crude product was dried using an oil pump (residual triethylamine!) and reacted without further purification.

^{1}H-NMR ($CDCl_3$): δ (ppm) 3.37 (s, 3H, NCH_3), 3.54 (s, 3H, OCH_3), 7.04-7.13 (m, 2H, 4-F-Ph), 7.71-7.78 (m, 2H, 4-F-Ph)

Example 21

2-(2-Chloropyridin-4-yl)-1-(4-fluorophenyl)ethanone (21a)

n-BuLi (15% strength solution in n-hexane, 45 ml, 104 mmol) was added dropwise to a solution, cooled to -85°C, of diisopropylamine (15 ml, 106 mmol) in abs. THF (150 ml) in a double-necked flask which had been dried by heating and flushed with argon: temperature increase to -50°C. After the addition had ended, the light-yellow solution was stirred at -85°C for 55 min. At -85°C, a solution of 2-chloro-4-methylpyridine (2-chloro-γ-picoline, 8.6 g; 68 mmol) in abs. THF (75 ml) was added dropwise to this initial charge: temperature increase to -50°C, initial change of color to purple. After the addition had ended, the reaction mixture was stirred at -85°C for 1 h, and a solution of **20** (12.4 g; 68 mmol) in abs. THF (75 ml) was added at this temperature over a period of 3 min: temperature increase to -60°C. The purple slurry of the reaction mixture was stirred at -85°C for 1 h and then, over a period of 1 h, warmed to 0°C. The mixture was poured into saturated NaCl solution (300 ml) which had been covered with ethyl acetate (300 ml). The organic phase was removed and the aqueous phase was extracted with ethyl acetate (2 × 250 ml) and a little brown foamy precipitate of 1,3-bis-(2-chloropyridin-4-yl)-2-(4-fluorophenyl)propan-2-ol separated off at the interface. The combined organic extract was washed with saturated NaCl solution, dried over $NaSO_4$ and concentrated. The oily residue was taken up in a little *tert*-butyl methyl ether and stored at 4°C overnight. The crystals were filtered off and dried.

^{1}H-NMR ($CDCl_3$): δ (ppm) 4.26 (s, 2H, CH_2), 7.11-7.26 (m, 4H, C^3-/C^5-H 2-Cl-Pyr and 4-F-Ph), 7.99-8.06 (m, 2H, 4-F-Ph), 8.35 (dd, 1H, 0.6/5.1 Hz, C^6-H 2-Cl-Pyr)

1-(4-Fluorophenyl)-2-(2-fluoropyridin-4-yl)ethanone (21b)

21b was prepared from 2-fluoro-4-methylpyridine (13.9 g; 125 mmol) using the method described in the synthesis of **21a**.

^{1}H-NMR ($CDCl_3$): δ (ppm) 4.32 (s, 2H, CH_2), 6.85-6.86 (m, 1H, C^3-H 2-F-Pyr), 7.08-7.19 (m, 3H, C^5-H 2-F-Pyr and 4-F-Ph), 8.00-8.07 (m, 2H, 4-F-Ph), 8.18 (d, 1H, 5.1 Hz, C^6-H 2-F-Pyr)

2-(2-Bromopyridin-4-yl)-1-(4-fluorophenyl)ethanone (21c)

21c was prepared from 2-bromo-4-methylpyridine (9.6 g; 56 mmol) using the method described in the synthesis of **21a**.

^{1}H-NMR ($CDCl_3$): δ (ppm) 4.35 (s, 2H, CH_2), 7.17-7.37 (m, 3H, 2-Br-Pyr and 4-F-Ph), 7.50 (s, 1H, C^3-H 2-Br-Pyr), 8.07-8.15 (m, 2H, 4-F-Ph), 8.42 (d, 1H, 5.1 Hz, C^6-H 2-Br-Pyr)

Example 22

1-(2-Chloropyridin-4-yl)-2-(4-fluorophenyl)ethane-1,2-dione-1-oxime (22a)

With stirring and cooling in a water bath (about 10°C), a solution of $NaNO_2$ (0.85 g; 12.3 mmol) in H_2O (10 ml) was added dropwise over a period of 2.5 min to a solution of **21a** (3.0 g; 12 mmol) in glacial acetic acid (30 ml). After the addition had ended, the reaction mixture was stirred at room temperature for 0.5 h, H_2O (60 ml) was added and stirring at room temperature was continued for 3 h. The light-beige precipitate was filtered off, washed with water and dried under reduced pressure over $CaCl_2$.

^{1}H-NMR (DMSO-d_6): δ (ppm) 7.34-7.52 (m, 4H, C^3-/C^5-H 2-Cl-Pyr and 4-F-Ph), 7.93-8.00 (m, 2H, 4-F-Ph), 8.47 (d, 1H, 5,2 Hz, C^6-H 2-Cl-Pyr), 12.71 (bs, 1H, exchangeable, OH)

1-(2-Fluoropyridin-4-yl)-2-(4-fluorophenyl)ethane-1,2-dione-1-oxime (22b)

22b was prepared from **21b** (10.0 g; 43 mmol) using the method described in the synthesis of **22a**.

^{1}H-NMR (DMSO-d_6): δ (ppm) 7.19-7.20 (m, 1H, C^3-H 2-F-Pyr), 7.35-7.47 (m, 3H, C^5-H 2-F-Pyr and 4-F-Ph), 7.91-7.98 (m, 2H, 4-F-Ph), 8.29 (d, 1H, 5.3 Hz, C^6-H 2-F-Pyr), 12.69 (s, 1H, exchangeable, OH)

1-(4-Fluorophenyl)-2-(2-isopropoxypyridin-4-yl)ethane-1,2-dione-2-oxime (22c)

A solution of **22b** (200 mg; 0.76 mmol) in HCl-saturated isopropanol (15 ml) was stirred under reflux for 2.5 h. The solution was concentrated and the yellowish-white residue was triturated with a little ethanol, filtered off and dried.

^{1}H-NMR (DMSO-d_6): δ (ppm) 1.24 (d, 6H, 6,2 Hz, 2 × CH_3), 5.15-5.27 (m, 1H, methyne-H), 6.54 (s, 1H, C^3-H 2-iso-O-Pyr), 7.08 (dd, 1H, 1,2/5.3 Hz, C^5-H 2-iso-O-Pyr), 7.36-7.49 (m, 2H, 4-F-Ph), 7.88-7.97 (m, 2H, 4-F-Ph), 8.19 (d, 1H, 5,4 Hz, C^6-H 2-iso-O-Pyr), 12.44 (bs, 1H, exchangeable, OH)

1-(2-Bromopyridin-4-yl)-2-(4-fluorophenyl)ethane-1,2-dione-1-oxime (22d)

22d was prepared from **21c** (5.0 g; 17 mmol) using the method described in the synthesis of **22a**.

^{1}H-NMR (DMSO-d_6): δ (ppm) 7.40-7.48 (m, 3H, C^3-H 2-Br-Pyr and 4-F-Ph), 7.65 (d, 1H, 0.8 Hz, C^5-H 2-Br-Pyr), 7.93-8.01 (m, 2H, 4-F-Ph), 8.45 (d, 1H, 5,2 Hz, C^6-H 2-Br-Pyr), 12.72 (bs, 1H, exchangeable, OH)

Example 23

2-Amino-2-(2-chloropyridin-4-yl)-1-(4-fluorophenyl)ethanone hydrochloride (23a)

With gentle heating, **22a** (1.5 g; 5.4 mmol) was dissolved in methanol (15 ml). The solution was cooled to room temperature, HCl-containing methanol (20 ml) was added and the mixture was transferred into a three-necked flask. Pd-C 10% (150 mg) was introduced into the initial charge. The reaction vessel was evacuated using an oil pump, and H_2 was then introduced via a gas inlet capillary (4 ×). At room temperature, the suspension was shaken in the closed three-necked flask under an atmosphere of H_2 (240 strokes/min) until no more starting material could be detected by thin-layer chromatography (6 h). The suspension was filtered and the catalyst was washed with plenty of methanol. The combined filtrate was concentrated and the mustard-colored solid-amorphous residue was dried using an oil pump. The crude product was used without further purification for the next reaction step.

^{1}H-NMR (DMSO-d_6): δ (ppm) 6.53 (bs, 1H, methyne-H), 7.35-7.45 (m, 2H, 4-F-Ph), 7.59 (dd, 1H, 1.5/5,2 Hz, C^5-H 2-Cl-Pyr), 7.85 (d, 1H, 0.9 Hz,C^3-H 2-Cl-Pyr), 8.17-8.25 (m, 2H, 4-F-Ph), 8.49 (d, 1H, 4,9 Hz, C^6-H 2-Cl-Pyr), 9.33 (bs, 3H, exchangeable, NH_3^+)

2-Amino-2-(2-fluoropyridin-4-yl)-1-(4-fluorophenyl)ethanone hydrochloride (23b)

With gentle heating, **22b** (5.0 g; 19 mmol) was dissolved in HCl-containing isopropanol (IsOH/HCl-saturated IsOH 1+1, 60 ml). The yellowish solution was cooled to room temperature and transferred into a three-necked flask (100 ml). Pd-C 10% (1.5 g) was introduced into the initial charge. The reaction vessel was evacuated using an oil pump and H_2 was then introduced via a gas inlet capillary (4 ×). At room temperature, the suspension was shaken in the closed three-necked flask under an atmosphere of H_2 (240 strokes/min) until no more starting material could be detected by thin-layer chromatography (6.5 h). The catalyst was filtered off. The filtration residue was washed with plenty of methanol (about 800 ml). The combined filtrates were

concentrated and the solid-amorphous residue was dried on an oil pump. The crude product was used without further purification for the next reaction step.

^{1}H-NMR (DMSO-d_6): δ (ppm) 6.58 (bs, 1H, methyne-H), 7.33-7.41 (m, 2H, 4-F-Ph), 7.54 (m, 2H, C^3-/C^5-H 2-F-Pyr), 8.14-8.25 (m, 2H, 4-F-Ph), 8.30 (d, 1H, 5.5 Hz, C^6-H 2-F-Pyr), 9.40 (bs, 3H, exchangeable, NH_3^+)

2-Amino-1-(4-fluorophenyl)-2-(2-isopropoxypyridin-4-yl)ethanone hydrochloride (23c)

23c was prepared from **22c** (2.0 g; 7.6 mmol) using the method described in the synthesis of **23a**.

^{1}H-NMR (DMSO-d_6): δ (ppm) 1.23 (d, 6H, 5.6 Hz, 2 × CH_3), 5.09-5.22 (m, 1H, methyne-H $CH(CH_3)_2$), 6.38-6,41 (bs, 1H, methyne-H CH-NH_3^+), 7.00-7.08 (m, 2H, 2-iso-O-Pyr), 7.33-7.46 (m, 2H, 4-F-Ph), 8.14-8.23 (m, 3H, 2-iso-O-Pyr and 4-F-Ph), 9.21 (bs, 3H, exchangeable, NH_3^+)

2-Amino-1-(4-fluorophenyl)-2-(2-methoxypyridin-4-yl)ethanone hydrochloride (23d)

23d was formed by treating **22b** (7.5 g; 29 mmol) under the conditions described in the synthesis of **23a**.

^{1}H-NMR (DMSO-d_6): δ (ppm) 3.83 (s, 3H, CH_3), 6.44 (bs, 1H, methyne-H), 7.13-7.16 (m, 2H, C^3-/C^5-H 2-MeO-Pyr), 7.34-7.46 (m, 2H, 4-F-Ph), 8.16-8.25 (m, 3H, C^6-H 2-MeO-Pyr and 4-F-Ph), 9.29 (bs, 3H, exchangeable, NH_3^+)

2-Amino-1-(4-fluorophenyl)-2-pyridin-4-ylethanone hydrochloride (23e)

23e was formed by treating **22c** (4.0 g; 12.4 mmol) under the conditions described in the synthesis of **23b**.

^{1}H-NMR (DMSO-d_6): δ (ppm) 6.78 (bs, 1H, methyne-H), 7.32-7.38 (m, 2H, 4-F-Ph), 8.07-8.13 (m, 2H, 4-Pyr), 8.17-8.27 (m, 2H, 4-F-Ph), 8.92-8.95 (m, 2H, 4-Pyr), 9.43 (bs, 3H, exchangeable, NH_3^+)

2-Amino-2-(2-bromopyridin-4-yl)-1-(4-fluorophenyl)ethanone hydrochloride (23f)

A solution of **22d** (1.8 g; 5.6 mmol) in absolute ethanol (30 ml) was cooled to -10°C, and concentrated sulfuric acid (1.3 ml) was added. With cooling, zinc dust (1.1 g) was added a little at a time to the initial charge. The reaction mixture was stirred at -10°C for 30 min and then warmed to room temperature. The gray-green suspension was filtered and the white residue ($ZnSO_4$) was washed with plenty of ethanol. The combined yellow filtrate was concentrated and the solid yellowish residue was dried using an oil pump.

^{1}H-NMR (DMSO-d_6): δ (ppm) 6.39 (bs, 1H, methyne-H), 7.35-7.44 (m, 2H, 4-F-Ph), 7.56 (dd, 1H, 1.4/5.1 Hz, C^5-H 2-Br-Pyr), 7.91 (s, 1H, C^3-H2-Br-Pyr), 8.12-8.19 (m, 2H, 4-F-Ph), 8.46 (d, 1H, 5.1 Hz, C^6-H2-Br-Pyr), 8.94 (bs, 3H, exchangeable, NH_3^+)

Example 24

4-(2-Chloropyridin-4-yl)-5-(4-fluorophenyl)-1,3-dihydroimidazole-2-thione (24a)

With gentle heating, **23a** (2.9 g; about 9.6 mmol) was dissolved in absolute DMF (75 ml). Potassium thiocyanate (1.9 g; 19.6 mmol) was introduced into the clear orange-red solution: immediate opalescence and a lighter color. The reaction mixture was stirred under reflux for 1.5 h. The suspension was cooled to room temperature and, with H_2O cooling, diluted dropwise with H_2O (about 140 ml). The yellow precipitate was filtered off, washed with H_2O and dried under reduced pressure over $CaCl_2$.

^{1}H-NMR (DMSO-d_6): δ (ppm) 7.12-7.52 (m, 6H, C^3-/C^5-H 2-Cl-Pyr and 4-F-Ph), 8.27 (d, 1H, 5,2 Hz, C^6-H 2-Cl-Pyr), 12.82 (bs, 2H, exchangeable, 2 × NH)

4-(4-Fluorophenyl)-5-(2-fluoropyridin-4-yl)-1,3-dihydroimidazole-2-thione (24b)

24b was prepared from **23b** (6.1 g; 20 mmol) using the method described in the synthesis of **24a**.

^{1}H-NMR (DMSO-d_6): δ (ppm) 7.12-7.16 (m, 2H, C^3-/C^5-H 2-F-Pyr), 7.28-7.27 (m, 2H, 4-F-Ph), 7.46-7.55 (m, 2H, 4-F-Ph), 8.13 (d, 1H, 5.1 Hz, C^6-H 2-F-Pyr), 12.85 (bs, 2H, exchangeable, 2 × NH)

4-(4-Fluorophenyl)-5-(2-isopropoxypyridin-4-yl)-1,3-dihydroimidazole-2-thione (24c)

24c was prepared from **23c** (2.5 g; 7.6 mmol) using the method described in the synthesis of **24a**.

^{1}H-NMR (DMSO-d_6): δ (ppm) 1.24 (d, 6H, 6,2 Hz, 2 × CH_3), 5.10-5.19 (m, 1H, methyne-H), 6.69-6.76 (m, 2H, 2-iso-O-Pyr), 7.24-7.32 (m, 2H, 4-F-Ph), 7.42-7.49 (m ,2H, 4-F-Ph), 8.02 (d, 1H, 5.5 Hz, C^6-H 2-iso-O-Pyr), 12.68 (bs, 2H, exchangeable, 2 × NH)

4-(4-Fluorophenyl)-5-(2-methoxypyridin-4-yl)-1,3-dihydroimidazole-2-thione (24d)

Potassium thiocyanate (2 g, 20.6 mmol) was introduced into a solution of **23d** (3.2 g; 10.8 mmol) in 10% strength hydrochloric acid (50 ml). The reaction mixture was stirred under reflux for 30 min. The orange solution was cooled and neutralized using 10% strength $NaHCO_3$ solution. The precipitate was filtered off, washed with H_2O and dried under reduced pressure over $CaCl_2$. The crude product was triturated with ethanol, and insoluble components were filtered off. On standing, **24d** precipitated from the ethanolic filtrate.

^{1}H-NMR (DMSO-d_6): δ (ppm) 3.81 (s, 3H, OCH_3), 6,79-6.82 (m, 2H, C^3-/C^5-H2-MeO-Pyr), 7.26-7.50 (m, 4H, 4-F-Ph), 8.06 (d, 1H, 5.3 Hz, C^6-H 2-MeO-Pyr), 12.65 (bs, 2H, exchangeable, 2 × NH)

Example 25

2-Chloro-4-[5-(4-fluorophenyl)-2-methylsulfanyl-3H-imidazol-4-yl]pyridine (25a)

Using the general method A, the title compound was obtained from **24a** (0.5 g; 1.6 mmol) and methyl iodide (0.35 g; 2.5 mmol) after a reaction time of 12 hours and purification by column chromatography (Al_2O_3, CH_2Cl_2/ethyl acetate 1+1). M.p. 236°C

IR (ATR): 3126, 3057, 2929, 1591, 1529, 1499, 1389, 1231 (C-F), 1159, 996, 976, 844, 780 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.62 (s, 1H, CH_3), 7.27-7.36 (m, 3H, 2-Cl-Pyr and 4-F-Ph), 7.45-7.55 (m, 3H, 2-Cl-Pyr and 4-F-Ph), 8.24 (d, 1H, 5.1 Hz, C^6-H 2-Cl-Pyr), 12.85 (bs, 1H, exchangeable, NH)

2-Fluoro-4-[5-(4-fluorophenyl)-2-methylsulfanyl-3H-imidazol-4-yl]pyridine (25b)

Using the general method A, the title compound was obtained from **24b** (0.95 g; 3.3 mmol) and methyl iodide (1.4 g; 9.9 mmol) after a reaction time of 40 hours. The crude product was boiled with CH_2Cl_2/ethyl acetate (1+1). The combined organic extract was decolorized using Al_2O_3, and the residue obtained after concentration of the filtrate was triturated with a little EtOH. M.p. 224°C

IR (ATR): 3073, 1609, 1497, 1421, 1234, 1219 (C-F), 1159, 1002, 883, 851, 833, 815 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.62 (s, 3H, CH_3), 7.08 (s, 1H, C^3-H 2-F-Pyr), 7.26-7.35 (m, 3H, C^5-H 2-F-Pyr and 4-F-Ph), 7.46-7.54 (m, 2H, 4-F-Ph), 8.08 (d, 1H, 5.3 Hz, C^6-H 2-F-Pyr), 12.85 (bs, 1H, exchangeable, NH)

4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3H-imidazol-4-yl]-2-isopropoxypyridine (25c)

NaH (55 - 65%; 1.0 g; about 23 mmol) was introduced into a solution of **24c** (4.0 g; 13.8 mmol) in absolute THF (60 ml). This initial charge was stirred at room temperature for 5 min, and a solution of methyl iodide (2.2 g; 17.3 mmol) in absolute THF (5 ml) was added dropwise with H_2O cooling. The reaction mixture was stirred at room temperature for 1 h. The clear brown solution was concentrated and the residue was taken up in H_2O. The aqueous solution was neutralized using 10% strength hydrochloric acid and extracted with ethyl acetate (2 ×). The combined organic extract was washed with saturated NaCl solution, dried over Na_2SO_4 and concentrated. The semi-solid residue was extracted by boiling with *tert*-butyl methyl ether (2 ×) and filtered. The clear ethereal filtrate was concentrated and the solid residue was triturated with a little *tert*-butyl methyl ether, filtered off and dried. Further reaction product was obtained by column chromatographic separation of the mother liquor (SiO_2 60, CH_2Cl_2/ethyl acetate 1+1). M.p. 141°C

IR (ATR): 2928, 1610, 1544, 1509, 1412, 1314, 1222 (C-F), 1104, 1005, 954, 865, 843, 816 cm^{-1}

^{1}H-NMR (CD_3OD): δ (ppm) 1.28 (d, 6H, 6,1 Hz, 2 × CH_3), 2.63 (s, 3H, SCH_3), 5.08-5.14 (m, 1H, methyne-H), 6.76 (s, 1H, C^3-H 2-iso-O-Pyr), 6.88 (dd, 1H, 1.4/5,4 Hz, C^5-H 2-iso-O-Pyr), 7.10-7.19 (m, 2H, 4-F-Ph), 7.40-7.47 (m, 2H, 4-F-Ph), 7.95 (dd, 1H, 0.7/5,4 Hz, C^6-H 2-iso-O-Pyr)

4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3H-imidazol-4-yl]-2-methoxypyridine (25d)

A solution of **24d** (1.0 g; 3.3 mmol) and methyl iodide (5.6 g; 39 mmol) in methanol (50 ml) was stirred under reflux for 3 h. The reaction mixture was cooled and filtered. The filtrate was concentrated and the residue was taken up in ethanol. Insoluble components were filtered off and the filtrate was concentrated. The residue was taken up in CH_2Cl_2/EtOH (9+1). Insoluble components were filtered off, and the fil-

trate was separated by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1). M.p. 158°C

IR (ATR): 1618, 1608, 1497, 1391, 1222 (C-F), 1212, 1036, 835, 825 cm^{-1}

^{1}H-NMR (CD_3OD): δ (ppm) 2.67 (s, 3H, SCH_3), 3.90 (s, 3H, OCH_3), 6.87-6.89 (m, 1H, C^3-H 2-MeO-Pyr), 6.98 (dd, 1H, 1.5/5.5 Hz, C^5-H2-MeO-Pyr), 7.16-7.24 (m, 2H, 4-F-Ph), 7.46-7.53 (m, 2H, 4-F-Ph), 8.03 (dd, 1H, 0.7/5.5 Hz, C^6-H 2-MeO-Pyr)

4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3H-imidazol-4-yl]-1H-pyridin-2-one (25e)

When **23d** (8.8 g; 31 mmol) was treated with potassium thiocyanate in boiling DMF analogously to the method described for **24a**, the only reaction product obtained was **25e**. M.p. 314°C (decomposition). After cyclization, giving the 1,3-dihydroimidazolethione, the methyl group from the methoxy substituent is transferred to the nucleophilic sulfur atom of the thione, with formation firstly of the 2-methylsulfanyl-3H-imidazole and, secondly, the 2-hydroxypyridine/1H-pyridin-2-one.

IR (ATR): 1634 (pyridone I), 1610, 1557 (pyridone II), 1493, 1220 (C-F), 968, 837, 800 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.61 (s, 3H, SCH_3), 6,16 (bs, 1H, C^3-H pyridone), 6,34 (s, 1H, C^5-H pyridone), 7.25-7.33 (m, 3H, C^6-H pyridone and 4-F-Ph), 7.46-7.53 (m, 2H, 4-F-Ph), 11,38 (bs, 1H, exchangeable, pyridone-NH), 12.71 (bs, 1H, exchangeable, imidazole-NH)

Benzyl-{4-[5-(4-fluorophenyl)-2-methylsulfanyl-3H-imidazol-4-yl]pyridin-2-yl}-amine (25f)

Using the general method C, the title compound was obtained from **25b** (0.2 g; 0.7 mmol) and benzylamine (0.8 g; 7.5 mmol) after a reaction time of 5 hours at 160°C and separation by column chromatography (Al_2O_3, CH_2Cl_2/ethyl acetate 1+1). M.p. 152°C (decomposition)

IR (ATR): 3234 (NH), 3006, 2916, 1601, 1583, 1501, 1451, 1432, 1353, 1225 (C-F), 1074, 844, 813, 729, 695 cm^{-1}

^{1}H-NMR (CD_3OD): δ (ppm) 2.59 (s, 3H, CH_3), 4.37 (s, 2H, CH_2), 6.56-6.59 (m, 2H, C^3-/C^5-H 2-amino-Pyr), 7.04-7.44 (m, 9H, Ph and 4-F-Ph), 7.83 (d, 1H, 5.6 Hz, C^6-H 2-amino-Pyr)

{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3H-imidazol-4-yl]pyridin-2-yl}-(4-methoxybenzyl)amine (25g)

Using the general method C, the title compound was obtained from **25b** (0.44 g; 1.5 mmol) and 4-methoxybenzylamine (2.0 g; 14.6 mmol) after a reaction time of 7 hours at 160°C and separation by column chromatography (SiO_2, CH_2Cl_2/EtOH 9+1). M.p. 207°C

IR (ATR): 1598, 1558, 1510, 1244, 1217 (C-F), 846, 812 cm^{-1}

^{1}H-NMR (CD_3OD): δ (ppm) 2.61 (s, 3H, SCH_3), 3.75 (s, 3H, OCH_3), 4.30 (s, 2H, CH_2), 6.56-6.59 (m, 2H, C^3-/C^5-H 2-amino-Pyr), 6.81-7.30 (m, 6H, 4-MeO-Ph and 4-F-Ph), 7.39-7.46 (m, 2H, 4-F-Ph), 7.84 (d, 1H, 6.0 Hz, C^6-H 2-amino-Pyr)

{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3H-imidazol-4-yl]pyridin-2-yl}-(4-methylbenzyl)amine (25h)

Using the general method C, the title compound was obtained from **25b** (0.2 g; 0.7 mmol) and 4-methylbenzylamine (0.85 g; 7.0 mmol) after a reaction time of 6 hours at 160°C and separation by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1). M.p.185°C

IR (ATR): 1600, 1559, 1502, 1427, 1218 (C-F), 844, 809 cm^{-1}

^{1}H-NMR (CD_3OD): δ (ppm) 2.29 (s, 3H, CH3), 2.60 (s, 3H, SCH3), 4.32 (s, 2H, CH2), 6.57-6.60 (m, 2H, C3-/C5-H 2-amino-Pyr), 7.05-7.50 (m, 8H, 4-Me-Ph and 4-F-Ph), 7.83 (d, 1H, 5.3 Hz, C6-H2-amino-Pyr)

(4-Chlorobenzyl)-{4-[5-(4-fluorophenyl)-2-methylsulfanyl-3H-imidazol-4-yl]-pyridin-2-yl}amine (25i)

Using the general method C, the title compound was obtained from **25b** (0.2 g; 0.7 mmol) and 4-chlorobenzylamine (1.0 g; 7.0 mmol) after a reaction time of 5.5 hours under reflux and separation by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1). M.p. 195°C

IR (ATR): 3409, 1597, 1549, 1502, 1489, 1422, 1218 (C-F), 843, 814, 793 cm^{-1}

^{1}H-NMR (CD_3OD): δ (ppm) 2.60 (s, 3H, SCH_3), 4.38 (s, 2H, CH_2), 6.57-6.60 (m, 2H, C^3-/C^5-H 2-amino-Pyr), 7.05-7.14 (m, 2H, 4-F-Ph), 7.22-7.30 (m, 4H, 4-Cl-Ph), 7.38-7.45 (m, 2H, 4-F-Ph), 7.83 (d, 1H, 5.7 Hz, C^6-H 2-amino-Pyr)

(3,4-Dichlorobenzyl)-{4-[5-(4-fluorophenyl)-2-methylsulfanyl-3H-imidazol-4-yl]-pyridin-2-yl}amine (25j)

Using the general method C, the title compound was obtained from **25b** (0.2 g; 0.7 mmol) and 3,4-dichlorobenzylamine (1.2 g; 6.8 mmol) after a reaction time of 7.5 hours at 160°C and separation by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1). M.p. 212°C

IR (ATR): 3409, 1600, 1552, 1509, 1490, 1424, 1225 (C-F), 842, 827, 813 cm^{-1}

^{1}H-NMR (CD_3OD): δ (ppm) 2.60 (s, 3H, SCH_3), 4.39 (s, 2H, CH_2), 6.56-6.62 (m, 2H, C^3-/C^5-H 2-amino-Pyr), 7.06-7.50 (m, 7H, 3,4-di-Cl-Ph and 4-F-Ph), 7.84 (d, 1H, 5.5 Hz, C^6-H 2-amino-Pyr)

{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3H-imidazol-4-yl]pyridin-2-yl}-phenylamine (25k)

Using the general method C, the title compound was prepared from **25b** (0.2 g; 0.7 mmol) and aniline (0.65 g; 7.0 mmol) after a reaction time of 6 hours under reflux and separation by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1). M.p. 228°C

IR (ATR): 3031, 1610, 1590, 1561, 1504, 1433, 1265, 1225 (C-F), 839, 827, 749, 695 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.62 (s, 3H, CH_3), 5.95-6.13 (m, 2H, C^3-/C^5-H2-amino-Pyr), 6.68-7.60 (m, 9H, Ph and 4-F-Ph), 7.97-8.01 (m, 1H, C^6-H 2-Amino-Pyr), 8.99 (bs, 1H, exchangeable, anilino-NH), 12.68 (bs, 1H, exchangeable, imidazole-NH)

{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3H-imidazol-4-yl]pyridin-2-yl}-phenethylamine (25l)

Using the general method C, the title compound was obtained from **25b** (0.2 g; 0.7 mmol) and 2-phenylethylamine (0.85 g; 7.0 mmol) after a reaction time of 5.5 hours at 160°C and separation by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1). M.p. 99°C

IR (ATR): 3409, 1604, 1546, 1504, 1220 (C-F), 838, 813, 698 cm^{-1}

^{1}H-NMR (CD_3OD): δ (ppm) 2.61 (s, 3H, SCH_3), 2.81 (t, 2H, 7.7 Hz, NCH_2), 3.41 (t, 2H, 7.7 Hz, CH_2Ph), 6.55-6.57 (m, 2H, C^3-/C^5-H 2-amino-Pyr), 7.08-7.26 (m, 7H, Ph and 4-F-Ph), 7.42-7.49 (m, 2H, 4-F-Ph), 7.82 (d, 1H, 6,1 Hz, C^6-H 2-amino-Pyr)

(RS)-{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3H-imidazol-4-yl]pyridin-2-yl}-(1-phenylethyl)amine (25m).

Using the general method C, the title compound was obtained from **25b** (0.2 g; 0.7 mmol) and *(RS)*-1-phenylethylamine (0.80 g; 6.6 mmol) after a reaction time of 7

hours at 160°C and separation by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1). M.p. 117 - 119°C

IR (ATR): 2926, 1607, 1547, 1502, 1434, 1221 (C-F), 1157, 838, 814, 699 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 1.37 (d, 3H, 5.5 Hz, CH_3), 2.58 (s, 3H, SCH_3), 4.82-5.03 (m, 1H, methyne-H), 6.39-7.74 (m, 12H, Ph, 2-amino-Pyr and 4-F-Ph), 12.57 (bs, 1H, exchangeable, NH)

(R)-{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3H-imidazol-4-yl]pyridin-2-yl}-(1-phenylethyl)amine (25n)

Using the general method C, the title compound was obtained from **25b** (0.2 g; 0.7 mmol) and *(R)*-1-phenylethylamine (0.80 g; 6.6 mmol) after a reaction time of 7 hours at 170°C and separation by column chromatography (SiO_2 60, CH_2Cl_2/ethyl acetate 1+1). M.p. 117 – 119°C

IR (ATR): 2926, 1607, 1547, 1502, 1434, 1221 (C-F), 1157, 838, 814, 699 cm^{-1}

^{1}H-NMR (CD_3OD): δ (ppm) 1.44 (d, 3H, 6.9 Hz, CH_3), 2.59 (s, 3H, SCH_3), 4.62-4.69 (m, 1H, methyne-H), 6,47-6.57 (m, 2H, C^3-/C^5-H2-amino-Pyr), 7.05-7.42 (m, 9H, Ph and 4-F-Ph), 7.80 (d, 1H, 5.5 Hz, C^6-H 2-amino-Pyr)

(S)-{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3H-imidazol-4-yl]pyridin-2-yl}-(1-phenylethyl)amine (25o)

Using the general method C, the title compound was obtained from **25b** (0.2 g; 0.7 mmol) and *(S)*-1-phenylethylamine (0.80 g; 6.6 mmol) after a reaction time of 13 hours at 170°C and separation by column chromatography (SiO_2 60, CH_2Cl_2/ethyl acetate 1+1). M.p. 117 – 119°C

IR (ATR): 2926, 1607, 1547, 1502, 1434, 1221 (C-F), 1157, 838, 814, 699 cm^{-1}

^{1}H-NMR (CD_3OD): δ (ppm) 1.44 (d, 3H, 6.9 Hz, CH_3), 2.59 (s, 3H, SCH_3), 4.62-4.69 (m, 1H, methyne-H), 6,47-6.57 (m, 2H, C^3-/C^5-H2-amino-Pyr), 7.05-7.42 (m, 9H, Ph and 4-F-Ph), 7.80 (dd, 1H, 0.5/5.5 Hz, C^6-H 2-amino-Pyr)

Benzyl-{4-[5-(4-fluorophenyl)-2-methylsulfanyl-3H-imidazol-4-yl]pyridin-2-yl}-methylamine (25p)

Using the general method C, the title compound was obtained from **25b** (0.2 g; 0.7 mmol) and N-methylbenzylamine (0.85 g; 7.0 mmol) after a reaction time of 7 hours at 180°C and two column-chromatographic separations (SiO_2 60, CH_2Cl_2/ethyl acetate 1+1). M.p. 79°C

IR (ATR): 2924, 1601, 1494, 1407, 1219 (C-F), 837, 810, 730, 696 cm^{-1}

^{1}H-NMR (CD_3OD): δ (ppm) 2.60 (s, 3H, SCH_3), 2.97 (s, 3H, NCH_3), 4.64 (s, 2H, CH_2), 6.64-6.66 (m, 2H, C^3-/C^5-H 2-amino-Pyr), 7.02-7.45 (m, 9H, Ph and 4-F-Ph), 7.96 (d, 1H, 5.0 Hz, C^6-H 2-amino-Pyr)

Example 26

4-[2-Benzylsulfanyl-5-(4-fluorophenyl)-3H-imidazol-4-yl]-2-chloropyridine (26a)

Using the general method A, the title compound was obtained from **24a** (0.3 g; 1.0 mmol) and benzyl chloride (0.12 g; 1.0 mmol) after a reaction time of 6 hours and purification by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9+1). M.p. 223°C

IR (ATR): 2939, 1591, 1530, 1505, 1233 (C-F), 997, 838, 782, 700 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 4.43 (s, 2H, CH_2), 7.27-7.47 (m, 11H, 2-Cl-Pyr, Ph and 4-F-Ph), 8.26 (d, 1H, 5.2 Hz, C^6-H 2-Cl-Pyr), 12.94 (bs, 1H, exchangeable, NH)

4-[2-Benzylsulfanyl-5-(4-fluorophenyl)-3H-imidazol-4-yl]-2-fluoropyridine (26b)

Using the general method A, the title compound was obtained from **24b** (5.1 g; 17.6 mmol) and benzyl bromide (9.2 g; 54 mmol) after a reaction time of 1.5 hours and separation by column chromatography (Al_2O_3, CH_2Cl_2/ethyl acetate 1+1). M.p. 174°C

IR (ATR): 3028, 2948, 1611, 1496, 1413, 1228 (C-F), 1203, 1003, 879, 838, 698 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 4.43 (s, 2H, CH_2), 7.11 (s, 1H, C^3-H 2-F-Pyr), 7.25-7.51 (m, 10H, C^5-H 2-F-Pyr, Ph and 4-F-Ph), 8.10 (d, 1H, 5.3 Hz, C^6-H 2-F-Pyr), 12.93 (bs, 1H, exchangeable, NH)

Benzyl-{4-[2-benzylsulfanyl-5-(4-fluorophenyl)-3H-imidazol-4-yl]pyridin-2-yl}-amine (26c)

Using the general method C, the title compound was obtained from **26b** (0.2 g; 0.53 mmol) and benzylamine (0.60 g; 5.6 mmol) after a reaction time of 6 hours at 180°C and separation by column chromatography (SiO_2 60, CH_2Cl_2/ethyl acetate 1+1). M.p. 185°C

IR (ATR): 3407 (NH), 3025, 2855, 2713, 1599, 1550, 1489, 1356, 1220 (C-F), 1155, 840, 814, 693 cm^{-1}

^{1}H-NMR (CD_3OD): δ (ppm) 4.21 (s, 2H, NCH_2), 4.38 (s, 2H, SCH_2), 6.52-6.55 (m, 2H, C^3-/C^5-H 2-amino-Pyr), 7.03-7.38 (m, 9H, Ph and 4-F-Ph), 7.83 (d, 1H, 5.7 Hz, C^6-H 2-amino-Pyr)

(RS)-{4-[2-Benzylsulfanyl-5-(4-fluorophenyl)-3H-imidazol-4-yl]pyridin-2-yl}-(1-phenylethyl)amine (26d)

Using the general method C, the title compound was obtained from **26b** (0.2 g; 0.53 mmol) and *(RS)*-1-phenylethylamine (0.65 g; 5.4 mmol) after a reaction time of 15 hours at 150°C and separation by column chromatography (SiO_2 60, CH_2Cl_2/ethyl acetate 1+1). M.p. 145°C

IR (ATR): 3028, 1606, 1546, 1494, 1450, 1221 (C-F), 1157, 837, 813, 697 cm^{-1}

^{1}H-NMR (CD_3OD): δ (ppm) 1.44 (d, 3H, 6.8 Hz, CH_3), 4.22 (s, 2H, CH_2), 6.44-6.54 (m, 2H, C^3-/C^5-H 2-amino-Pyr), 7.04-7.35 (m, 9H, Ph and 4-F-Ph), 7.80 (d, 1H, 5.4 Hz, C^6-H 2-amino-Pyr)

{4-[2-Benzylsulfanyl-5-(4-fluorophenyl)-3H-imidazol-4-yl]pyridin-2-yl}-(4-methoxybenzyl)amine (26e)

Using the general method D, the title compound was obtained from **26a** (0.2 g; 0.5 mmol) and 4-methoxybenzylamine (2.0 g; 14.6 mmol) after a reaction time of 22 hours under reflux and separation by column chromatography (Al_2O_3, CH_2Cl_2/ethyl acetate 1+1). M.p. 196 - 200°C

IR (ATR): 1605, 1574, 1507, 1245, 1225 (C-F), 843, 814, 698

^{1}H-NMR (DMSO-d_6): δ (ppm) 4,29 (s, 2H isomers "A" + "B", NCH_2), 4.35 (s, 2H "A" + "B", SCH2), 6.43-6.47 (m, 1H "A" + 2H "B", C^5-H "A" and C^3-/C^5-H "B" 2-amino-Pyr), 6.65 (s, 1H "A", C^3-H2-amino-Pyr), 6.80-6.84 (m, 2H "A" + "B", 4-MeO-Ph), 7.14-7.51 (m, 11H "A" + "B", 4-MeO-Ph, Ph and 4-F-Ph), 7.79 (d, 1H "B", 5.4 Hz, C^6-H 2-amino-Pyr), 7.91 (d, 1H "A", 5.4 Hz, C^6-H 2-amino-Pyr), 12.67 (bs, 1H, exchangeable, Imidazole-NH), amino-NH not visible

4-[2-Benzylsulfanyl-5-(4-fluorophenyl)-3H-imidazol–4-yl]-2-methoxypyridine (26f)

A suspension of **25a** (0.1 g; 0.25 mmol) in methanolic $NaOCH_3$ solution (30%, 2 ml) was diluted with methanol (5 ml) and stirred under reflux for 13 h. The reaction mixture was diluted with H_2O and the aqueous solution was extracted with CH_2Cl_2 (3×). The combined organic extract was washed with saturated NaCl solution, dried over Na_2SO_4 and concentrated. The oily residue was purified by column chromatography (SiO_2 60, CH_2Cl_2/ethyl acetate 1+1).

^{1}H-NMR ($CDCl_3$): δ (ppm) 3.91 (s, 3H, OCH_3), 4.29 (s, 2H, CH_2), 6.91-6.95 (m, 1H, 2-MeO-Pyr), 7.02-7.11 (m, 2H, 4-F-Ph), 7.27-7.38 (m, 7H, Ph and 4-F-Ph), 8.05 (d, 1H, 5,4 Hz, C^6-H 2-MeO-Pyr), NH not visible

Example 27

2-Chloro-4-[5-(4-fluorophenyl)-2-(4-methanesulfinylbenzylsulfanyl)-3H-imidazol-4-yl]pyridine (27a)

NaH (55 – 65%; 0.1 g; about 2 mmol) was introduced into a solution of **24a** (0.31 g; 1.0 mmol) in absolute THF (15 ml). The initial charge was stirred at room temperature for 5 min, and 4-methylsulfinylbenzyl chloride (**3,** 0.19 g; 1.0 mmol) was added. The reaction mixture was stirred at room temperature for 2 h. The yellow-brown solution was diluted with H_2O and neutralized with 10% strength citric acid. The THF was removed and the aqueous solution was extracted with ethyl acetate (2 ×). The combined organic extract was washed with saturated NaCl solution (2 ×), dried over Na_2SO_4 and concentrated. The solids residue was purified by column chromatography (SiO_2 60, CH_2Cl_2/EtOH 9.5+0.5). M.p. 179°C

IR (ATR): 3049, 1592, 1505, 1374, 1224 (C-F), 1086, 1030 (S=O), 1014, 989, 839, 816, 781 cm^{-1} (C-Cl)

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.71 (s, 3H, CH_3), 4.48 (s, 2H, CH_2), 7.25-8.24 (m, 10H, 2-Cl-Pyr, 4-MeS(O)-Ph and 4-F-Ph), 8.26 (d, 1H, 5.3 Hz, C^6-H 2-Cl-Pyr), 12.94 (bs, 1H, exchangeable, NH)

2-Fluoro-4-[5-(4-fluorophenyl)-2-(4-methanesulfinylbenzylsulfanyl)-3H-imidazol-4-yl]pyridine (27b)

Using the general method A, the title compound was obtained from **24b** (4.2 g; 14.5 mmol) and **3** (4.1 g; 22 mmol) after a reaction time of 2 hours and separation by column chromatography (1. Al_2O_3, CH_2Cl_2/ethyl acetate 1+1, 2. SiO_2 60, CH_2Cl_2/EtOH 9+1). M.p. 150°C

IR (ATR): 3061, 1610, 1506, 1408, 1227 (C-F), 1030 (S=O), 1016, 995, 978, 882, 839, 815 cm^{-1}

^{1}H-NMR (DMSO-d_6): δ (ppm) 2.71 (s, 3H, CH_3), 4.49 (s, 2H, CH_2), 7.10 (s, 1H, C^3-H2-F-Pyr), 7.30-7.37 (m, 3H, C^5-H 2-F-Pyr and 4-F-Ph), 7.47-7.67 (m, 6H, 4-F-Ph and 4-MeS(O)-Ph), 8.11 (d, 1H, 4,8 Hz, C^6-H 2-F-Pyr), 12.95 (bs, 1H, exchangeable, NH)

Benzyl-{4-[5-(4-fluorophenyl)-2-(4-methanesulfinylbenzylsulfanyl)-3H-imidazol-4-yl]pyridin-2-yl}amine (27c)

Using the general method C, the title compound was obtained from **27b** (0.3 g; 0.68 mmol) and benzylamine (0.75 g; 7.0 mmol) after a reaction time of 7 hours at 170°C and separation by column chromatography (SiO_2 60, CH_2Cl_2/ethanol 19+1). M.p. 149°C

IR (ATR): 3238, 3064, 1600, 1558, 1514, 1495, 1227 (C-F), 1034 (S=O), 1006, 982, 839, 814 cm^{-1}

^{1}H-NMR (CD_3OD): δ (ppm) 2.70 (s, 3H, CH_3), 4.21 (s, 2H, NCH_2), 4.32 (s, 2H, SCH_2), 6.51-6.55 (m, 2H, C^3-/C^5-H 2-amino-Pyr), 7.03-7.42 (m, 13H. Ph, 4-MeS(O)-Ph and 4-F-Ph), 7.82 (d, 1H, 5.5 Hz, C^6-H 2-amino-Pyr)

(RS)-{4-[5-(4-Fluorophenyl)-2-(4-methanesulfinylbenzylsulfanyl)-3H-imidazol-4-yl]pyridin-2-yl}-(1-phenylethyl)amine (27d)

Using the general method C, the title compound was obtained from **27b** (0.3 g; 0.68 mmol) and *(R*S)-1-phenylethylamine (0.85 g; 7.0 mmol) after a reaction time of 10 hours at 170°C and separation by column chromatography (SiO_2 60, CH_2Cl_2/ethanol 9+1). M.p. 193°C

IR (ATR): 2967, 1606, 1547, 1502, 1221 (C-F), 1085, 1031 (S=O), 1014, 838, 814, 670 cm^{-1}

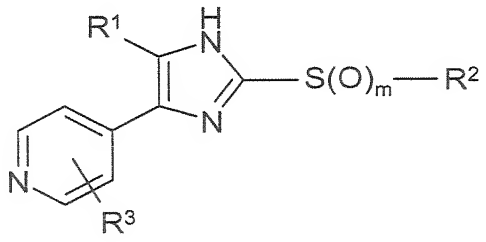
^{1}H-NMR (CD_3OD): δ (ppm) 1.45 (d, 3H, 6.8 Hz, CH_3), 2.67 (s, 3H, $S(O)CH_3$), 4.28 (s, 2H, CH_2), 4.62-4.73 (m, 1H, methyne-H), 6.42-6.53 (m, 2H, C^3-/C^5-H 2-amino-Pyr), 7.09-7.44 (m, 9H, Ph and 4-F-Ph),), 8.21 (d, 1H, 5.0 Hz, C^6-H 2-F-Pyr).

5

259/sg

WE CLAIM

1. A 2-thio-substituted imidazole derivative of the formula I



in which

R^1 is C_1-C_6-alkyl, C_3-C_7-cycloalkyl or aryl which is unsubstituted or substituted by a halogen atom;

R^2 is selected from the group consisting of

a) aryl-C_1-C_4-alkyl, where the aryl radical may have one, two or three substituents independently of one another selected from the group consisting of C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, C_1-C_6-alkylsulfanyl, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl and hydroxyl, and

b) C_1-C_6-alkyl which is unsubstituted or substituted by CN; and

c) C_3-C_7-cycloalkyl;

R^3 is selected from the group consisting of

a) NR^4R^{10}

b) NR^7COR^8,

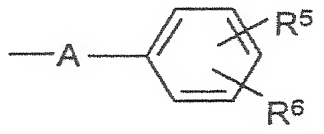
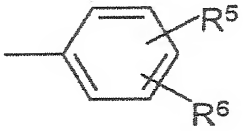
c) halogen and

d) C_1-C_6-alkoxy,

e) C_1-C_6-alkylthio-

where R^3 is not OH, halogen, C_1-C_6-alkylthio or C_1-C_6-alkoxy if R^2 is phenyl-C_1-C_4-alkyl and the phenyl radical has a C_1-C_6-alkylsulfanyl, C_1-C_6-alkylsulfinyl or C_1-C_6-alkylsulfonyl substituent;

R^4 is H;

R^{10} is  or 

R^5 and R^6, which may be identical or different, are H, halogen, C_1-C_6-alkoxy or C_1-C_6-alkyl;

R^7 is H, C_1-C_6-alkyl or benzyl;

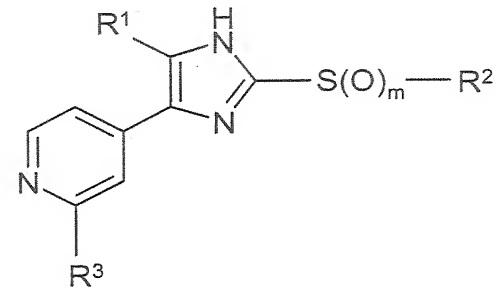
R^8 is C_1-C_4-alkyl, C_3-C_6-cycloalkyl or phenyl, it being possible for the phenyl group to have one or two substituents which are chosen independently from one another from the group consisting of C_1-C_4-alkyl, C_1-C_4-alkoxy and halogen;

A is straight-chain or branched C_1-C_6-alkylene, C_2-C_6-alkenylene or C_3-alkynylene and

m is 0, 1 or 2;

and the tautomers, optical isomers and physiologically acceptable salts thereof.

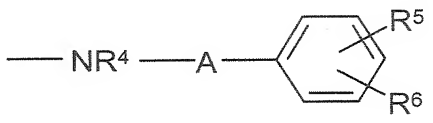
2. The compound as claimed in claim 1 of the formula Ia



Ia

in which R^1, R^2, R^3 and m are as defined in claim 1.

3. The compound as claimed in claim 1 or 2 where R^3 is



where A, R^5 and R^6 are as defined in claim 1.

4. The compound as claimed in any of the preceding claims where A is C_1-C_2-alkylene.

5. The compound as claimed in any of the preceding claims where A is ethylidene.

6. The compound as claimed in claim 5 where R^5 and R^6 are H.

7. The compound as claimed in any of the preceding claims where R^1 is halogen-substituted phenyl.

8. The compound as claimed in any of the preceding claims where R^2 is benzyl or C_1-C_6-alkyl.

9. A pharmaceutical composition, comprising at least one compound as claimed in any of claims 1 to 8, if appropriate together with one or more pharmaceutically acceptable carriers and/or additives.

10. The use of at least one compound as claimed in any of claims 1 to 8 for preparing a pharmaceutical composition for treating disorders associated with a disturbed immune system.

11. A method for treating disorders associated with a disturbed immune system, characterized in that an amount of a compound of the formula I as claimed in any of claims 1 to 8 sufficient to have immunomodulating action and/or to inhibit the release of cytokine is administered to a person in need of such a treatment.

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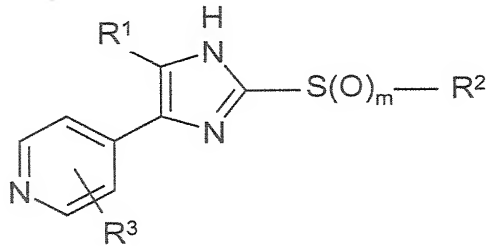
Abstract

The invention relates to 2-thio-substituted imidazole derivatives of the formula I



in which the radicals R^1, R^2, R^3 and m are as defined in the description. The compounds according to the invention have immunomodulating and/or cytokine-release-inhibiting action and are therefore suitable for treating disorders associated with a disturbed immune system.